Practical chemotherapy of malaria

Report of a
WHO Scientific Group

Technical Report Series
805

World Health Organization, Geneva 1990

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WHO SCIENTIFIC GROUP ON THE CHEMOTHERAPY OF MALARIA

Geneva, 5–12 June 1989

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PRACTICAL CHEMOTHERAPY OF MALARIA

Report of a WHO Scientific Group

A WHO Scientific Group on the Chemotherapy of Malaria met in Geneva from 5 to 12 June 1989. The meeting was opened on behalf of the Director-General by Dr T. Bektimirov, Assistant Director-General.

INTRODUCTION

From the most recent information obtained by the World Health Organization, it is estimated that 2073 million people (over 40% of the world's population), living in more than 100 countries, are exposed to the risk of malaria and that some 270 million of these are infected with malaria parasites. While the number of cases *reported* to WHO has been of the order of 5 million annually for the past three years (a total that excludes figures from the WHO African Region owing to the insufficiency and irregularity of reports from countries of the Region), the best estimate is that perhaps 110 million clinical cases occur every year, of which 90 million are in tropical Africa. Global deaths are estimated at approximately 1 million a year, but this figure seems low in the light of studies in a number of countries. The situation in the world as a whole is far from improving, even though the annual incidence seems to have been falling in some countries, notably China and India.

It is the complexity of malaria that has enabled it to resist so successfully the many and varied attempts to eradicate or control it. With this in mind, and recognizing that the worldwide eradication of the disease is not an attainable goal in the foreseeable future, the WHO Expert Committee on Malaria in 1985 (*1*) promoted an epidemiological approach to the design of control operations: priorities for action and for the orientation of control should be determined by the local epidemiological situation rather than by general control axioms. The main objective should be to provide easily accessible and appropriate diagnostic and treatment facilities for the whole population in a malarious area. This is considered a

necessary minimum to meet the most basic health requirements of the population.

Previous WHO Scientific Groups on the Chemotherapy of Malaria have regularly provided recommendations on the use of the antimalarial drugs available at the time they met (*2, 3*), but rapidly changing epidemiological patterns and their variability even within a country make the provision of common guidelines for WHO's Member States a difficult task. As long ago as 1937, L.W. Hackett (*4*) remarked: "Clearly governments can trust no formulas devised in Geneva or elsewhere, but must create the simple machinery necessary to define and resolve their own problems, locality by locality." His remark is still pertinent today, although the complexity of the disease will not necessarily allow simple mechanisms for the resolution of the problems.

This report, then, attempts to provide the technical information required by antimalarial programmes to establish and evaluate, in their particular situations, the recommendations for the use of drugs that the present Scientific Group puts forward. The report discusses the factors that need to be considered in developing and implementing a policy on the use of drugs in malaria and briefly reviews current practices in the diagnosis of the disease. In addition to the central sections on the management and treatment of individual patients suffering from uncomplicated or severe malaria, topics such as estimating the amount of antimalarial drugs necessary, their procurement, and systems for monitoring are also considered. A separate section deals with new antimalarials under development. The report is addressed primarily to middle-level planners and administrators who are responsible for a malaria service, but others such as research workers, clinicians, and primary health planners may find it a useful guide to understanding the factors that influence the choice of drugs for the treatment of malaria.

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1. GENERAL CONSIDERATIONS FOR THE DEVELOPMENT OF A MALARIA TREATMENT POLICY

1.1 Epidemiological considerations

Malaria is a major problem in situations of two distinct types: (1) where the transmission is seasonal or focal and the level of acquired immunity in the general population is not great; and (2) where the disease is holoendemic, the transmission stable and intense, and much of the adult population has a considerable degree of acquired immunity.

The first-mentioned type is found in, for instance, much of South-East Asia and South and Central America, in particular in areas where endemic malaria was considerably reduced or even eliminated as a result of large-scale control measures, but in which transmission has subsequently been reinstated, and in zones affected by major ecological or social changes, such as those due to agricultural or other economic exploitation of jungle or forest areas or to sociopolitical unrest. While these areas contain only about 1% of the world's population, they concentrate some of the most severe malaria problems.

The second type occurs mainly where antimalaria programmes were never effectively implemented and the endemicity remains basically unchanged, as in much of tropical Africa.

The aims of treatment will necessarily vary in these two extreme epidemiological situations. In areas of stable, intense transmission, the majority of deaths occur in the early years of life, when the passive immunity acquired from the mother has waned and the infant has not yet developed sufficient immunity of its own to protect itself. At this age, prompt life-saving treatment is required. In older patients, on the other hand, a drug that produces a temporary diminution in parasitaemia may be satisfactory for limiting the illness and allowing the immune system of the individual to control the infection. However, though symptomatic malaria in adults is unusual in these holoendemic areas, it does occur and must be treated vigorously.

In contrast, where malaria is seasonal or focal and there is little acquired immunity, everyone may be at risk of death from uncontrolled parasitaemia, and treatment to eliminate both the overt disease and the infecting parasite is required. In such situations, it is often the adults who are at greatest risk. In many areas in Asia, for

example, persons living where transmission is restricted to the forest may have a limited risk of infection for most of their early lives, their first exposure occurring when they start work that brings them into the forest in adolescence or early adulthood. Infection in this situation is as life-threatening as it is for African children after the loss of maternal immunity. Similarly, migrants or refugees from a malaria-free area who move into an area of transmission will require vigorous treatment of their infections and must be identified as a high-risk group.

In any epidemiological situation, the severity of the illness is also markedly influenced by the species of *Plasmodium* causing the malaria. *Plasmodium vivax, P. ovale* and *P. malariae* rarely produce life-threatening diseases, unlike *P. falciparum*, which frequently causes severe disease and all too often death.

The presence of drug-resistant *P. falciparum* is a further complicating factor. Resistance can vary in prevalence, intensity, and clinical significance. The number of countries reporting some degree of resistance of *P. falciparum* to antimalarial drugs has increased markedly in the past decade, to the extent that very few countries where this parasite occurs have not yet recorded resistance. In some areas, however, the resistance is local and of low degree, so that chloroquine remains operationally effective; in many others, widespread high-level resistance has made this drug unusable.

1.2 Malaria services

In any setting, the primary aims of the treatment of malaria are to prevent death from the disease and to alleviate symptoms as promptly as possible. Ideally, this should be the responsibility of the general health services, guided by a fully coordinated malaria service or programme, with a core of experts on the epidemiology, chemotherapy, and control technology aspects.

The degree of development and integration of the malaria service and the general health services influences the ways in which treatment is oriented and implemented. Vertical antimalaria programmes, where they exist, may work in total isolation from the general health services, in cooperation with them, or, rarely, as an integral part of them. They may be well organized and effective, poorly organized but better than nothing (particularly where the peripheral general health services are understaffed and short of supplies), or they may be frankly counterproductive (where they

have become bureaucracies preoccupied with self-preservation). Where malaria treatment has become part of the general health services, it may be supported by the remnants of a good system of malaria training and supervision; it may benefit by integration with a well organized health system; or it may be submerged in a poorly designed and poorly implemented general system (*1*). In realistic planning for the identification and treatment of malaria cases, all these factors must be kept in mind as they affect the selection of drugs and regimens and the complexity of follow-up schemes.

Specialized, single-purpose "malaria clinics" have proved successful when they have been established in peripheral areas where there is a high risk of severe malaria. Malaria is diagnosed microscopically in these clinics and appropriate treatment, generally free, is given immediately to the patient. However, the establishment of efficient, coordinated, peripheral services is difficult. When they exist, their accessibility to patients may be severely limited, because there are few of them, because they are inappropriately sited, or for a number of other reasons. Even when they are accessible, patients may prefer not to use them: the supply or quality of drugs may be inadequate, resulting in a loss of confidence in the services, or the attitudes of the health workers staffing them may deter utilization. These factors must be kept in mind when estimates of malaria prevalence are based on hospital or health centre statistics and attempts are made to identify risk groups from these data. Very biased notions of the extent of endemicity, of the groups at highest risk, or of the prevailing level of malaria mortality can result from reliance on such information (*2*).

Many health services continue to pursue aims far broader than simply the prevention of morbidity and mortality. Some countries, for example, have retained—from the attack phase of former malaria eradication programmes—an exaggerated emphasis on the organization and implementation of residual house-spraying with insecticides, mass drug treatment being accessory to this activity and aimed primarily at reducing the parasite reservoir. Diagnosis and treatment of suspected malaria cases served, in many eradication campaigns, to identify and eliminate foci of continuing transmission during the consolidation phase. Primaquine, for instance, was used to eliminate gametocytes of *P. falciparum* and to effect radical cure of *P. vivax* infections in an attempt to prevent the re-establishment of transmission when it had been stopped or reduced to a very low level. However, the routine inclusion in standard treatment regimens

of gametocytocidal doses of primaquine cannot be expected to make a sufficient impact on transmission when only a minority of parasitaemic individuals is actually receiving such doses through the malaria or general health services, the remainder seeking other sources of treatment.

Some extraordinarily complex systems with rigid hierarchies were created in the attempt to eradicate malaria. In many countries where the disease remains a serious public health problem, these systems persist, with attention to diagnosis and treatment remaining secondary to grander but possibly unrealistic objectives. Both in these systems and elsewhere, the approaches to diagnosis and treatment may be largely managerial, and the choice of drugs to be used is often based solely on considerations of cost. The primary criteria for the selection of antimalarial drugs should be efficacy, safety, acceptability, availability, and the degree of development of the health infrastructure.

1.3 Treatment targets and regimens

It is obvious that target populations of high-risk individuals should be identified in order to focus treatment activities, but too often targets are inappropriately or too broadly defined. Health planning officials, for example, may decide that young children are a special high-risk group and malaria treatment, or even prophylaxis, may be aimed at those attending maternal and child health (MCH) clinics. This may, in fact, be an inappropriate response based on too superficial an evaluation and planning process, since MCH clinics are mainly in urban areas, where children may be at much lower risk than rural children. If attention and resources are focused on an ill-defined goal, the children at greatest real risk may suffer even further.

Moreover, when patients, particularly in areas of unstable malaria, make their initial contact with the health service, fully effective therapy is required. Treatment that is merely palliative can be fatal. Individuals may have gone to great expense and inconvenience to travel great distances for treatment; if they return home after receiving an inadequate drug, they may be unable to afford a second treatment when the first fails; immunity may be insufficiently stimulated to limit the course of the infection and death may be the outcome.

It is wrong for malaria services to select operational treatment regimens solely on the results of limited clinical or hospital trials without validating their relevance to the field. Often patients treated in hospitals, particularly teaching hospitals that conduct clinical research, are not typical of the population served by the malaria programme. They are generally more severely ill; they may have been treated unsuccessfully elsewhere; or they may have developed complications before they or their families decided on a difficult journey to the central hospital, possibly involving a critical delay. Patients who patronize hospitals, especially central hospitals, may also differ in education, sophistication, or affluence from the typical recipient of peripheral malaria services; judgements based on their understanding of or compliance with a regimen may be misleading.

In addition, conditions in any hospital are markedly different from those facing the vast majority of outpatients. Nursing supervision may ensure the effective administration of long or complex drug regimens, which may be totally inappropriate for unsupervised use. For example, in a study in Thailand a regimen of quinine every 8 hours for 3 days plus tetracycline every 6 hours for 7 days produced an almost 100% cure rate in hospitals but less than 70% cures in malaria clinics, even when the dosing times were synchronized (S. Pinichpongse, personal communication, 1989). This unacceptable lack of efficacy was due to poor compliance, probably related to the complexity of the regimen, as well as to the unpleasant side-effects of quinine. In addition, the wide-scale use of quinine treatment, most of which was probably in incomplete courses, seems to have resulted in a decrease in *in vitro* sensitivity of *P. falciparum* to both quinine and mefloquine in the parts of the country where the quinine/tetracycline regimen was most extensively used and before mefloquine was ever used operationally in the country (*3*).

The presence of drug-resistant *P. falciparum* presents health planners with the difficult problem of deciding when it is necessary to change drug regimens at the various levels of the health services. Often a change has been dictated simply by the recording of resistance to the drug being used, coupled with pressure from various sectors, such as doctors, the press, government officials or pharmaceutical concerns. Unfortunately, such pressure may be lent support by a superficial interpretation of the problem and the distribution of resistance. The situation in reality is more complex. Many factors must be considered when deciding whether a change

is necessary, among them being: the degree of resistance, the epidemiological situation, the availability of alternative drugs at the periphery, their safety, the level of training required for their competent use, costs, possible interactions with other drugs that are commonly used for fever and malaria, and the infrastructure of the referral system.

(See recommendations 9.1.2 and 9.1.3.)

1.4 Patterns of drug use

In many malarious countries, chloroquine and other antimalarial drugs are widely available on the open market and are taken as self-medication without diagnosis. The availability of the same drug under different brand names may cause considerable confusion in self-medication and delay in seeking treatment. A person may, for instance, start self-medication with one brand of chloroquine and, when the condition does not improve, switch to another brand marketed under a different name by a different company. In the meantime, the illness may have progressed almost to the point of irreversibility. The fact that the tablets may be of different sizes and in different packaging may also suggest to the layman that they are different drugs. It is extremely important to recognize that antimalarial drugs are being widely used in this *ad hoc* fashion nearly everywhere that malaria occurs.

There is also a risk of toxic reactions following self-medication. Often a patient treated by the malaria service or the general health services with drugs such as amodiaquine or a combination of sulfadoxine and pyrimethamine will have already used the same drugs for self-medication, having obtained them from a drug store, as leftover medication from a relative or friend, or from some other source. In this way, the patient may have received several treatment doses in a relatively short time. Such use may be equivalent to prophylaxis, in which amodiaquine or combinations containing long-acting sulfonamides have been associated with serious side-effects (*4*). Therefore, the expectation that such drugs will be safe if they are used by a malaria programme *only* for the treatment of symptomatic cases is highly unrealistic. In countries where hundreds of thousands or even millions of people annually receive a drug from the health services, even a frequency of severe reactions as low as 1 in 5000–8000 (as for sulfadoxine/pyrimethamine) will mean that large numbers of people are at risk (*5*).

Similar considerations may apply to the routine administration of parenteral loading doses of chloroquine or quinine. Both drugs may be safe in the absence of previous treatment, but both may be dangerous in the presence of a pre-existing high blood level of either the same drug or a pharmacodynamically similar one. A survey in Zaire indicated that 92% of children who presented at a hospital emergency ward had detectable blood levels of chloroquine or quinine at the time that they were seen by a health worker (*6*). Such considerations underscore the urgency for the development and application of simple, quick tests for the presence of antimalarial drugs in urine.

1.5 Instructions to health workers

When planning treatment regimens for use at all levels of health services, it is essential that simple and clear instructions are given to the health worker. This is particularly true at the periphery, where the dispensing staff generally have only a basic education and a minimum of health training. The complex information that peripheral health workers are expected to assimilate is often daunting.

Even in single-purpose malaria clinics, it is difficult for the health workers to understand the important differences between the various species of *Plasmodium* that cause malaria, particularly that *P. falciparum* infections cause serious, life-threatening illness, whereas *P. vivax* infections may be comparable to a bout of flu, even though initially they both may cause similar acute illness. Thus the worker who may have only a few months' training must understand the urgency of treating patients diagnosed as having *P. falciparum* infections and ensure that drugs are actually swallowed and retained. He or she must realize that the patient must be referred immediately if there are any signs of severity, and make sure that the patient can get to the referral centre and is not simply discharged from the clinic. This alone is a heavy burden without the additional one of understanding the reasons for and intricacies of administration of a complex regimen.

The problem is even greater where the support of a timely parasitological diagnosis is lacking and where health centre staff or health volunteers are required to diagnose and treat malaria on clinical grounds. The selection of understandable regimens and

provision of clear, easily comprehensible guidelines for their use are crucial in such situations.

1.6 Changing policies

When a decision is made to change the recommendations for antimalarial drug regimens, it is important to keep its operational implications in mind. Even in the industrialized world, where medical publications abound and communication is easy, it is very difficult to bring information on changes in drug policy to the attention of medical practitioners. The problem is tremendously compounded in developing countries, in which communications may be difficult and dispensers relatively untrained. Even in countries with a vertical malaria service and relatively well trained and supervised field staff, it probably takes two years to implement a change in drug regimens to the point at which a fair degree of understanding exists at the periphery.

A policy for the treatment of malaria at the periphery must therefore take into account the following considerations:

—the status of the existing general health and antimalarial services;
—the efficiency and effectiveness of malaria information systems;
—the risks and benefits of the drug regimens;
—the feasibility of introducing new regimens, including availability, cost, and acceptability of the relevant drug or drugs;
—the difficulties involved in changing to new recommendations, such as those arising from the time lag between making a recommendation and its implementation at all levels of the health services.

(Recommendation 9.1.1; see also recommendation 9.1.4.)

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2. SOME ASPECTS OF DIAGNOSIS

2.1 Diagnostic requirements and practices

The appropriate management of malaria starts with the decision that an ill person has malaria. This decision—the diagnosis—may be made by professional health care personnel at the first-referral or village level, by a lay health person, by a family member or by the patient himself. It is often assumed that malaria diagnoses rest upon the recognition of a clearly defined clinical syndrome—usually involving fever—and the results of laboratory examinations, including microscopical diagnosis; yet in many settings such findings are not made, nor would they always be useful. The complex interactions of malaria infections with other tropical disease conditions require that emphasis be placed on identifying those persons who will benefit from antimalarial drug therapy—i.e., an operational diagnosis.

2.1.1 *Assessment of symptoms*

Assessment of clinical symptoms is an imprecise means of diagnosis in malaria. Investigations conducted in tropical Africa showed that only about 46% of patients so diagnosed actually had parasitaemia; in addition, some 15% of patients clinically diagnosed as suffering from fevers due to other diseases were, in fact, proved to have plasmodial infections (*1, 2*). Another study showed that the incidence of several major symptoms of malaria (rigor, sweating, headache, backache, nausea, vomiting, and diarrhoea) as well as the mean body temperature did not vary significantly between malarial and nonmalarial patients (*3*). Moreover, the body temperature may

not help in making the diagnosis in areas of stable and hyper- and holoendemic malaria, since reinfections occur continually from infancy, producing temperature variations with no particular pattern or periodicity.

Nevertheless, the presence of fever or a recent history of fever is a crucial factor in the diagnosis of malaria and many other diseases in tropical countries. In many settings, it is important to provide practical guidelines on the management of the febrile patient. Simple diagnostic and treatment charts or algorithms are needed to integrate the important, treatable causes of fever. Such charts would not be disease-specific but would, rather, help in the recognition of the practical constraints to patient management and would emphasize operational decisions. Many febrile patients, even in areas of high malaria endemicity, present with symptoms consistent with a number of diseases that are treatable though life-threatening. It is important, therefore, to develop a differential clinical diagnosis for use in a variety of clinical situations; for example, tachypnoea and fever are indicative of respiratory tract infections, neck stiffness and fever of meningitis, and pyrexia in pregnancy and the puerperium of uterine, urinary tract or breast infection.

Acute febrile illness during the malaria season in a high-risk age group, such as pregnant women and children under 5 years old in holoendemic areas, or associated with particular occupations (e.g., gem miners on the Thai-Cambodian border) or with a history of recent travel into a known transmission area may be strongly correlated with malaria infection and serves as a pointer to diagnosis.

It must become more widely recognized that, in many parts of the world, clinical diagnosis and management constitute the only available approach to the malaria problem for the near future and that clinical management is a valid measure in itself and not merely a stopgap until laboratory facilities can be made available. Clearly, clinical diagnosis will be nonspecific in many instances and will result in the treatment of some febrile illnesses that are not malaria; this is inevitable if the objective of limiting malaria morbidity and mortality is to be attained. However, the tendency, noted in some areas, to treat *all* febrile illnesses as malaria leads to excessive exposure of patients to potentially toxic antimalarials. In addition, equating fever with malaria may result in patients with treatable nonmalarial fevers not receiving adequate diagnosis or therapy. It is important, therefore, that a systematic approach be taken in order

to ensure the highest possible degree of sensitivity and specificity of diagnosis irrespective of the method used.

(See recommendation 9.2.1.)

2.1.2 *Laboratory services*

In areas of stable and intense malaria transmission—much of tropical Africa and Papua New Guinea, for instance—the high level of immunity acquired quite early in life results in a high prevalence of minimally symptomatic infections. Over 90% of these are due to *P. falciparum* and there is often only limited correlation between the level of parasitaemia and the clinical condition of the patient. In this situation, microscopical diagnosis may not be particularly useful in indicating which illnesses need treatment. There are, however, epidemiological situations in which a special effort should be made to ensure that facilities for microscopical diagnosis are available. These are areas of unstable malaria—as in many parts of Asia and South America—where there is an approximately even proportion of *P. vivax* and *P. falciparum* infections and where, owing to multiple drug resistance in the latter parasite, the preferred therapies of the two infections involve very different drugs. Here laboratory diagnosis is essential for adequate case management.

In the case of epidemics of unknown cause, portmortem microscopical examination of needle autopsy material from the brain or of heart blood smears may implicate or exclude malaria.

The provision and maintenance of laboratory services are expensive and must be guided by careful evaluation of health services to ensure efficient and effective health care delivery. Ideally, these facilities should be polyvalent, but even if at first they deal only with malaria (where this is the predominant cause of morbidity and mortality), they can be expanded later to provide information and guidance on the appropriate management of other conditions. In any event, the appropriate management of severe and complicated illness requires the support of laboratory services in all epidemiological situations. Evaluation of possible malaria therapy failures should also include examination of a blood smear whenever possible. It is evident that the extended use of microscopical diagnosis of assured quality would improve the targeting of antimalarial drugs, reducing the frequency of unnecessary side-effects and diminishing the wastage of often expensive drugs.

Microscopical diagnosis is often a routine in control programmes in areas of unstable malaria in which health services are fairly well developed. Communications are also, on the whole, comparatively efficient and cheap so that referral systems can be more easily maintained. In some countries, the integration of services has increased the responsibilities of the health workers and reduced support and supervision; while in others vertical malaria programmes are still in operation, which makes training and supervision of microscopists easier.

In Thailand, an effective vertical malaria programme is linked to the basic health services with adequate financial support from the Government, supplemented by bilateral aid programmes. The diagnostic facilities currently available at the various levels in that country are as follows:

(*a*) At the village level, blood films are taken by volunteers, who also give partially effective "presumptive therapy". Slides are collected by malaria workers every few days and examined at the laboratory. Appropriate specific treatment for positive cases is provided subsequently by the malaria workers, but the time between blood collection and definitive treatment is often much too long.

(*b*) At the district level, each district in malarious regions almost always has a "malaria clinic", a single-purpose facility which is open 5–7 days a week, depending on the endemicity. A slide is made and examined microscopically, and specific treatment is provided, usually within 30–45 minutes. Many districts have hospitals to which severely ill or vomiting patients can be referred for parenteral therapy.

(*c*) At the regional level, cross-checking of slides taken at the village and district levels is performed and the training support and supervision of microscopists are organized.

Thus microscopical diagnosis can be carried out at the peripheral level of the health services in many circumstances. It can be efficient, but it is costly (*3*).

(See recommendations 9.2.2–9.2.4.)

2.2 Diagnosis by light microscopy

Microscopical examination of thick blood smears, dehaemoglobinized and Giemsa-stained, allows for the differentiation of the *Plasmodium* species responsible for a malaria infection. The

examination of thin blood smears, fixed and Giemsa-stained, permits better species differentiation and provides information on haematological parameters but is much less sensitive and may miss low-grade infections. For the routine diagnosis of malaria, standardization makes it possible to obtain an adequate estimate of the number of circulating parasites per microlitre of blood and thus of the intensity of infection. A limited amount of equipment is required: mainly a light microscope and facilities for preparing stained blood films. Although microscopical diagnosis can be carried out at the peripheral level of health services, it is evident that, without the maintenance of training, supervision and support, the mere provision of microscopes and other equipment at this or any other level will not always yield reliable diagnoses and the treatment given may therefore not be appropriate (*4*).

At present, the microscopes and materials provided at the peripheral level for malaria diagnosis are not always chosen with a clear understanding of the functions they have to perform, the practical constraints imposed by their technical specifications, and the conditions under which they have to be used. Consequently the selection of light microscopes and other resources is a matter for careful consideration in order to ensure that they are used to their full potential. The principal technical constraint is the provision of a cheap, reliable light source for adequate illumination of binocular microscopes under all field conditions. Manufacturers should be encouraged to provide a suitable means, based on modern technology, of overcoming this constraint.

Other problems and constraints at the peripheral level, however, must not be ignored. For example, training is expensive and requires efficient organization for the selection of suitable candidates, for the preparation of courses, and for refresher training. The equipment too, needs proper maintenance and supplies (e.g., immersion oil and staining materials) which have to be provided routinely, and this requires an effective infrastructure.

A falsely optimistic confidence is also often placed on microscopists working at the peripheral level. Even when their efficiency is not impaired by a lack of supplies and poor maintenance and training, they must frequently examine 100 slides a day, a tedious task that often results in low-density parasitaemias being missed and in unreliable species diagnoses.

Any attempt to extend the laboratory network is futile if the quality of the work is not acceptable. Basic training must be

supplemented by regular supervision and refresher courses. Ideally, any country in which a laboratory network is considered important should possess a reference laboratory. In addition to checking "difficult" or "important" slides sent in from the periphery and exercising quality control on diagnoses carried out at the periphery, it should train personnel and control the quality of training at other centres. If a reference laboratory does not already exist, it should preferably be established at an institution where training and cross-checking of blood slides already take place. The possibility of using research laboratories for this purpose should be considered.

2.3 Risks associated with the taking of blood for smears or sampling

Human immunodeficiency virus (HIV) and other infectious pathogens can be transmitted from an infected to an uninfected person by the repeated use for blood sampling of lancets, needles and similar "sharps" that have not been fully cleaned and sterilized. The WHO Global Programme on AIDS estimates the risk of HIV infection following a finger-prick with a needle contaminated with HIV-positive blood at 0.13–0.5% (*5*), and the Centers for Disease Control, in the USA, have estimated the risk of transmitting hepatitis B virus to unvaccinated persons at between 6% and 30% (*6*). The number of people in malarious countries at risk of accidental infections of this sort has not been calculated but, considering the size of the world population exposed to malaria and the numbers from whom a drop of blood is routinely drawn for a smear, it must be enormous. To this should be added the corresponding risk to the field and laboratory staff who handle potentially infectious equipment and samples.

As far as possible, therefore, invasive techniques should be avoided and the taking of blood samples for routine surveillance minimized. In many cases, existing records could provide, although with more effort and difficulty, much of the epidemiological or statistical information that is currently sought from fresh finger-prick or venepuncture blood samples.

However, when an invasive technique is justified by the direct benefit to the patient, biosafety can be improved by simple changes in routine practices. Proper presterilization of the material to be used should be ensured and its safe disposal carefully planned and executed in accordance with accepted procedures (*5, 6*). All health

workers should be fully trained in these procedures and adequately supervised to ensure continued compliance.

The common practice of using Hagedorn needles or, worse, syringe needles to make serial skin punctures of large numbers of patients should be forbidden, since resterilization of the needles between each use is extremely difficult to achieve and to monitor effectively. The use of disposable lancets should become the norm, and if skin pricking is reduced to the essential minimum, the costs involved will be comparatively small when set against the cost of processing blood samples for diagnosis or analysis. The potential cost in human suffering and to the health services resulting from inadequate preventive measures hardly requires elaboration here.

Ideally, disposable blood lancets and needles should be used for taking blood films once only and then disposed of in a safe manner, using standard techniques laid down for the safe disposal of potentially hazardous waste. If nondisposable lancets and needles have to be used, they should be sterilized following each single use. These instructions should be routinely disseminated to all levels of health workers and supervisory measures established to ensure that proper preventive procedures are fully observed.

The risk of such auto-infections can also be reduced by targeting and minimizing the taking of blood samples for routine surveillance and by the training of all health staff in the appropriate methods to protect themselves from bloodborne infections. It is desirable to coordinate the implementation of adequate, preventive measures and seek support from other programmes, such as those for AIDS control, that are particularly concerned with the control of the spread of disease by adventitious infections.

(See recommendation 9.2.5.)

References (Section 2)

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3. THE MANAGEMENT AND TREATMENT OF UNCOMPLICATED MALARIA

3.1 Principles of therapy

3.1.1 *Evaluation*

General clinical features in patients with malaria should be assessed to determine the appropriate diagnostic and therapeutic action required for effective management. Among these are the following:

Hydration status: Hyperpyrexia, vomiting, diarrhoea, and anorexia contribute to the dehydration encountered in patients with malaria. Adequate rehydration and the assurance of fluid intake are important determinants of clinical recovery, especially in young children.

Ability to take oral medication. Vomiting may complicate the therapy of malaria, especially in children. Vomiting associated with high fever is frequently a criterion for parenteral therapy but experience shows that, in a substantial proportion of febrile children, oral therapy will be possible within 1–2 hours after reduction of fever.

Anaemia. Anaemia frequently occurs in uncomplicated malaria. If the anaemia has clinically compromised the patient, therapy is required to ensure adequate cardiovascular function. Frequently, this can be accomplished with the infusion of colloidal solutions. Blood transfusion, with its inherent risks, should be reserved for severely anaemic patients in situations where the availability of safe blood can be ensured.

Central nervous system function. The presence of central nervous system changes should prompt consideration of treatable but potentially lethal conditions such as hypoglycaemia and cerebral malaria (see sections 4.5.3 and 4.5.4).

3.1.2 *Assessment of prior therapy*

It is important to determine whether a patient has already been treated with antimalarial drugs. This may be done by carefully obtaining a medical history or by chemical screening of body fluids. Patients who are parasitaemic and are likely to have received treatment within the previous 3–7 days may have been "treatment failures". Those who have been treated with drugs within the previous 24–36 hours may be at risk of adverse drug interactions if other drugs are administered. All such patients should subsequently be monitored carefully.

3.1.3 *Selection of therapy*

The objectives of malaria chemotherapy should be defined for each patient. In many settings, the main objective for an uncomplicated *P. falciparum* infection is to provide a schizontocide that will lower parasite density and relieve illness; even in this situation, however, some patients at special risk may require chemotherapy that provides radical cure, although they may not have severe or complicated disease. Examples of such patients are:

—pregnant women (see section 3.4);
—people who have had repeated, frequent malaria attacks, particularly if there is a suspicion of treatment failure; and
—people suffering from concurrent serious disease, such as severe anaemia (see section 3.6.3), pneumonia, or malnutrition.

3.2 Antimalarial drugs

The chemical structures, properties, pharmacokinetics, metabolism, and toxic effects of the standard antimalarial drugs have been described in detail in earlier publications (*1, 2*). The following account is therefore brief and concentrates on current practice and recent knowledge.

3.2.1 *Chloroquine*

3.2.1.1 *Efficacy*. Chloroquine is usually given orally in a 3-day course for the curative treatment of chloroquine-sensitive *P. falciparum* and *P. malariae* and for termination of an acute attack of *P. vivax* or *P. ovale* malaria. The standard regimen consists of 10 mg

base per kg of body weight followed by 5 mg/kg 6–8 hours later and 5 mg/kg on each of the second and third days. A more practical regimen used in many areas consists of 10 mg base/kg on the first and second days and 5 mg/kg on the third. Both these regimens provide a total dose of 25 mg/kg (1500 mg base for a 60-kg adult); although the former can be regarded as pharmacokinetically superior, experience indicates that it has no practical advantage over the simpler regimen.

There is no evidence that increasing the dose of chloroquine increases the clinical cure rate in areas of developing chloroquine-resistant falciparum malaria (*3*) and repeated administration of high doses can produce adverse effects. Cumulative doses of 1 g/kg or between 50 g and 100 g in total have been associated with retinal damage, but there is great individual variability (*4*). Frequent therapeutic doses could result in such levels.

No abortifacient or teratogenic effects have been reported with chloroquine and so it may be considered safe in pregnancy. However, when the objective of treatment is radical cure of relapsing malaria, a course of primaquine, in addition to chloroquine, is required to eliminate hypnozoites in the liver, but primaquine should not be administered to pregnant women because of the potential damage to the fetus (see section 3.2.6.2).

3.2.1.2 *Toxicity*. Adverse effects related to chloroquine are rare and mild when the drug is given orally in the usual antimalarial doses. Nausea and vomiting may occur if it is taken on an empty stomach. Headache and difficulty in visual accommodation have been reported in patients receiving a therapeutic regimen of 25 mg/kg. Pruritus of the palms, soles and scalp has been reported in up to 20% of Africans using chloroquine, more frequently in adults than in children; it is not relieved by antihistamines. It is also common among Haitians and some dark-skinned population groups in Asia. All these symptoms are reversible upon discontinuation of the medication. Other side-effects include photoallergic dermatitis, pigmentation of the skin, leukopenia, bleaching of the hair, and, very rarely, aplastic blood disorders (*4*).

Acute poisoning may occur after oral ingestion of a single amount as low as 1.5–2.0 g. Half this amount may be fatal in children. Symptoms of poisoning include headache, nausea, diarrhoea, dizziness, muscular weakness, and blurred vision. Circulatory failures

may occur. Severe poisoning has been treated successfully by intensive hospital care and high-dose diazepam and isoprenaline (*5*).

3.2.2 *Amodiaquine*

With the expansion of chloroquine resistance in most areas of the world, there has been a marked increase in the use of amodiaquine both for initial therapy and for the treatment of chloroquine failures. This practice is based primarily on the observation that amodiaquine may be more effective at clearing parasitaemia in areas where chloroquine resistance of high degree is encountered (*6, 7*). The therapeutic advantage is slight, however, in that the proportion of total parasitological cures is approximately the same with the two drugs. Amodiaquine, like chloroquine, also causes pruritus.

Evidence accumulated during the past four years shows that amodiaquine can produce toxic hepatitis and potentially lethal agranulocytosis (*8–11*). The frequency of such adverse reactions has been estimated to be 1 in 2000, with death occurring in 1 in 15 000 users. Most of the reactions have occurred when amodiaquine was used for chemoprophylaxis and in many cases after very few doses, which might be simulated by repeated amodiaquine therapy of malaria in endemic settings. In view of the risks associated with amodiaquine and its limited therapeutic advantages, amodiaquine should not be used for prophylaxis or treatment either as a first-line drug or even as a more restricted alternative for chloroquine failures.

(See recommendation 9.3.1.)

3.2.3 *Quinine*

3.2.3.1 *Efficacy.* The extension of chloroquine-resistant *P. falciparum* has prompted an increase in the need for quinine for the management of patients. It is administered either orally or by injection at a dose of 10 mg salt per kg of body weight given 3 times a day for periods up to 10 days. Certainly, quinine is one of the most valuable antimalarial drugs available because of its rapid schizontocidal action in most malarious areas.

Decreasing sensitivity to quinine has been detected in some areas, such as in Thailand, in which it has been used extensively for malaria therapy. This has occurred particularly when therapy was given in an unsupervised and ambulatory setting and involved regimens longer than 3 days (*12*). Experience shows that patient compliance with

such regimens is low and that only a small proportion of patients complete the full course of prescribed therapy. Such incomplete treatment in patients who remain parasitaemic favours the selection of parasites less sensitive to quinine. It is of concern that there has appeared to be a degree of cross-resistance between quinine and mefloquine, suggesting that the wide-scale use of quinine might influence the future efficacy of the other valuable drug (*13*).

3.2.3.2 *Toxicity*. A syndrome of characteristic adverse reactions known as "cinchonism" occurs in many patients taking quinine: giddiness, light-headedness, transient hearing loss, tinnitus, amaurosis, or blurred vision may appear at therapeutic blood concentrations of 5–10 ng/ml (*4*). Anorexia, nausea, and vomiting may occur after the first few doses, although these may be difficult to distinguish from the symptoms of acute malaria. Quinine has also been associated with diarrhoea and abdominal pain in clinical trials conducted in Thailand. The symptoms enumerated seldom necessitate discontinuation of therapy. Electrocardiographic changes consisting primarily of delayed atrioventricular conduction and bradycardia and, rarely, atrioventricular block have also been observed at therapeutic blood concentrations. Quinine may potentiate the orthostatic (postural) hypotension due to malaria.

Less frequent but more serious side-effects of quinine include urticaria, asthma, thrombocytopenia, haemolysis, and oedema of the eyelids, mucous membranes and lungs. These may occur following a single dose and necessitate immediate discontinuation of the drug. Drug fever has also been observed to accompany the administration of quinine. In one study, 10% of United States soldiers in Viet Nam treated with a 10-day regimen of quinine were observed to develop fevers unexplained by other causes; these fevers generally began on the eighth day of treatment (*14*). Hypoglycaemia due to malaria may be aggravated by oral treatment even with low doses of quinine, as a result of stimulation of insulin secretion (*15*); this is a particularly important consideration in the treatment of malaria in pregnant women, whose blood glucose should be carefully monitored.

Quinine has been considered dangerous in pregnancy. Recent work, however, suggests that therapeutic doses do not induce labour and that the stimulation of contractions and evidence of fetal distress associated with the use of quinine may be more properly attributed to the presence of fever and other effects of the malaria itself (*16*).

3.2.3.3 *Use of quinine*. Quinine remains the preferred treatment for chloroquine-resistant malaria in many countries. However, the need for prolonged courses, which give rise to a high frequency of side-effects (some potentially dangerous) and consequently to poor compliance, suggests that it should, whenever possible, be used under supervision in hospital or where outpatients can be monitored.

The optimal use of quinine is to be derived from taking advantage of its rapid schizontocidal action, which is most important in the first few days of therapy. Radical cure can be achieved most effectively by administering a 2–4 day course of quinine (10 mg/kg of body weight, 8-hourly), to produce clinical improvement, with another effective oral schizontocide, such as tetracycline or a sulfadoxine/pyrimethamine combination. This can reduce the quinine-related side-effects, making for better compliance. A combination of quinine (10 mg/kg, 8-hourly, for 3 days) with 7 days of tetracycline (adult dose 250 mg, 6-hourly) is an effective regimen.

It should be recognized, however, that there are circumstances in which extended courses of quinine may be indicated to achieve parasitological cure. These include settings in which there is resistance to the oral schizontocides that might be associated with quinine or in which their use may be contraindicated. (This is the case, for instance, with tetracycline, which is not suitable for pregnant women and children under 8 years of age; see section 3.2.7.1). The longer courses of quinine, however, raise the problem of poor compliance. Research is therefore needed to develop other combinations of quinine that might be effective in shorter courses and be suitable for all types of patient.

3.2.4 *Quinidine*

Early studies suggested that quinidine, the dextrorotatory diasterioisomer of quinine, was superior to quinine as an antimalarial drug. Recent studies of oral quinidine sulfate tablets (*17, 18*) and quinidine slow-release preparations (*19*) have indicated that these formulations are effective and without untoward toxicity. A double-blind comparison of oral quinine and quinidine in uncomplicated falciparum malaria in Thailand showed that quinidine produced a significantly higher cure rate (*18*). Quinidine has a similar spectrum of side-effects to quinine but it is more expensive and more likely to cause cardiac effects, such as

arrhythmias, and hypersensitivity reactions (*20*). It is therefore not recommended as an alternative to quinine unless quinine is not available.

(See recommendation 9.4.4.)

3.2.5 *Mefloquine*

Mefloquine, a quinolinemethanol chemically related to quinine, is a potent, long-acting blood schizontocide active against parasites resistant to 4-aminoquinolines, to sulfonamide/pyrimethamine combinations, and to quinine. It is effective in a single oral dose (usually 3 or 4 tablets) and so avoids the patient compliance problems associated with quinine/tetracycline combinations, another effective regimen for the treatment of multidrug-resistant infections. Mefloquine, both as a monosubstance and in a combination with sulfadoxine/pyrimethamine, was first registered in Switzerland in 1984. Subsequently these formulations have been registered in several other countries.

At present there is no parenteral formulation of mefloquine since the drug has been shown to be very irritating to the peripheral vasculature. The drug has been administered as an aqueous suspension via intragastric tube to patients who are unable to tolerate oral medication, but intragastric administration has produced inadequate and erratic blood levels in severely ill patients with cerebral malaria (*21*).

3.2.5.1 *Dosage.* In Thailand, where the average adult body weight is approximately 50 kg, a single oral dose of 750 mg (15 mg/kg) is used. This dose has, until very recently, consistently produced cure rates in the field of over 90%.

Tolerance studies in healthy male volunteers and in malaria patients showed that side-effects such as dizziness, nausea and vomiting (see below) occurred with increasing frequency as the dose of mefloquine exceeded 1000 mg base (*22*). Thus, 15 mg of mefloquine base per kg of body weight, up to a maximum of 1000 mg, should be regarded as the optimal adult dose.[1] A divided dose of mefloquine may decrease the gastrointestinal intolerance, but

[1] Data from non-immune subjects weighing more than 60 kg are insufficient to conclude that this regimen will result in radical cure in all cases.

the added benefits of certainty of compliance with outpatient administration of a single dose outweigh the advantage of lesser side-effects. In view of the potential central nervous system toxicity (see section 3.2.5.2), and until it is clear whether this toxicity is dosage-related, higher doses must be used with caution, even in heavy patients. The dosage for children should also be 15 mg/kg, but further studies are required to assess the efficacy of this regimen in young children.

3.2.5.2 *Toxicity.* The main adverse reactions reported following the use of mefloquine are dizziness or a disturbed sense of balance, nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite. In general, these effects are mild to moderate, self-limiting, do not require specific treatment, and occur with a frequency similar to that of reactions to other antimalarial drugs. Severe dizziness, however, has been reported in certain individuals; there is some evidence that this reaction may be related both to the dose of mefloquine and to the speed with which the drug is absorbed and therefore to its peak plasma concentration. Individual variation in the pharmacokinetics and metabolism of the drug, as well as the fact that these side-effects are also indicative of malaria, makes it difficult to interpret these relationships, and this is an area that requires urgent study.

Asymptomatic sinus bradycardia was a constant finding in clinical trials conducted in Thailand (*23*) and in Zambia (*24*). In all cases, the pulse rate decreased 3–4 days after drug administration but returned to normal within 14 days. Dose-related sinus arrhythmia was also observed in 40–60% of adults treated in Thailand with 750–1250 mg of mefloquine, either as the mono-substance or in combination with pyrimethamine/sulfadoxine (T. Harinasuta, personal communication). A number of children studied also exhibited exaggerated sinus arrhythmia following mefloquine administration but it was not clear if this was drug-related (*25*). (See section 3.2.5.4.)

No haematological or biochemical abnormalities related to drug administration have been documented in any of the patients treated with mefloquine in clinical trials (*22*). There has, however, been increasing concern about reports of serious adverse neurological and psychiatric effects following both the therapeutic and prophylatic use of mefloquine. The first report of such side-effects was from a clinical trial in Zambia in 1980, but since then other reports have been received from controlled clinical trials (*23, 24, 26–28*), surveys

of travellers, and spontaneous reports to both the manufacturers and WHO (*29–31*). These reactions have ranged from fatigue and asthenia to seizures and acute psychosis and have been reported following the use of both mefloquine alone and in fixed combination with sulfadoxine and pyrimethamine. They have been reported following the administration of doses ranging from 500 to 2000 mg of mefloquine or 2–3 tablets of the triple combination. More severe side-effects have been reported following the administration of treatment doses of 1000 mg and above, although the frequency at all doses is difficult to calculate owing to the small number of cases and the lack of valid denominators. Although serious neurological and psychiatric events have not been reported from prophylactic drug trials, there have been spontaneous reports, relating to events the more serious of which appeared to take place after 3–5 weeks of prophylaxis.[1]

(See recommendations 9.3.3 and 9.3.4.)

3.2.5.3 *Mefloquine/sulfadoxine/pyrimethamine combination.* When mefloquine first became available for operational treatment of malaria, a recommendation was made that it should only be used in association with another effective antimalarial in order, theoretically, to delay the selection of mefloquine-resistant parasites (*1*). This recommendation was based on the finding in the *P. berghei*/mouse model that resistance to mefloquine developed more slowly when additive combinations were applied than when mefloquine was used alone (*33, 34*). The choice of a partner drug was difficult because of the very long elimination half-life of mefloquine—up to 33 days in healthy volunteers, although it may be significantly shorter in patients with falciparum malaria (*35*). The synergistic combination of mefloquine with sulfadoxine and pyrimethamine, which have plasma half-lives of 8 and 4 days respectively, was chosen.

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[1] Subsequent to the meeting of the Scientific Group, the World Health Organization convened an informal consultation on the subject of neurological side-effects associated with mefloquine use. Considering the documented evidence of the occurrence of dizziness and vertigo that may disturb coordination and spatial perception following the prophylactic use of mefloquine, the consultation recommended "that persons involved in tasks requiring fine coordination and spatial discrimination (e.g., air crews) not use mefloquine for prophylaxis, and avoid such tasks for a period of time following therapeutic use" (*32*).

More recently, there have been reasons to reconsider this recommendation. Sulfadoxine/pyrimethamine, when used for prophylaxis, has been associated with a frequency of severe cutaneous reactions of 1 in 5000–8000 in the USA (*36*) and of 1 in 2600–10 800 in the United Kingdom (*37*). This reaction may be fatal in 1 out of 11 000–25 000 persons using the combination for prophylaxis (*36*). When the triple combination of mefloquine/sulfadoxine/pyrimethamine was used for treatment in Thailand, 12 cutaneous reactions, two of which were severe, were reported following the administration of approximately 79 000 therapeutic doses of the drug. No fatal reactions were reported, but one child who had earlier taken a treatment dose of sulfadoxine/pyrimethamine was left with a scarred cornea from ocular involvement (*38*).

Recent studies in the same country have also shown that mefloquine and mefloquine/sulfadoxine/pyrimethamine are equally effective in the treatment of acute uncomplicated *P. falciparum* infections, both in the malaria clinics (S. Pinichpongse, personal communication) and in the central hospital (T. Harinasuta, personal communication). There was, however, a greater frequency of gastrointestinal side-effects following the administration of the triple combination than with mefloquine alone.

In the light of these observations, the triple combination of mefloquine with sulfadoxine and pyrimethamine is no longer recommended for either treatment or prophylaxis.

(Recommendation 9.3.2.)

3.2.5.4 *Drug interactions*. Extreme caution must be exercised in the use of mefloquine in patients concurrently taking beta-blockers, calcium-channel blockers, digitalis or antidepressants until further convincing evidence is available on the interaction of mefloquine with cardioactive agents. The cardioactive effect of other antimalarials such as quinine or quinidine may also be aggravated in the presence of mefloquine. Drug interaction studies between mefloquine and many other widely used drugs are not complete and therefore any patients receiving additional medication must be closely observed. In addition, medications used for symptomatic relief in *P. falciparum* malaria, such as antiemetics and diazepam, should be used with caution in patients treated with mefloquine.

3.2.6 *Primaquine*

3.2.6.1 *Efficacy*. Primaquine is highly active against gametocytes and against the hypnozoites (latent liver stages) of relapsing malarias, but has little blood schizontocidal activity. As a gametocytocide for *P. falciparum*, it is effective at a single dose of 30–45 mg base. The usual dose for antirelapse therapy of *P. vivax* and *P. ovale* is 15 mg base daily for 14 days (*4*). However, radical cure of *P. vivax* in most of South-East Asia and Oceania requires higher total doses of primaquine. This can often be accomplished by extending the 15 mg base/day regimen to 21 days.

(See recommendations 9.3.5 and 9.3.6.)

3.2.6.2 *Toxicity*. Although toxic symptoms are rare when primaquine is given at the usual dosage, higher doses may be accompanied by gastrointestinal complaints, such as anorexia, nausea, epigastric distress, vomiting, and abdominal pain and cramps. These may be accompanied by vague symptoms such as weakness and uneasiness in the chest.

The more severe side-effects at the higher doses of primaquine are related to its effect on the formed elements of the blood and bone marrow, resulting in leukopenia, anaemia, suppression of myeloid activity, and methaemoglobinaemia. Primaquine does not produce granulocytopenia at the dosage normally used for the treatment of malaria. High doses, however, particularly when accompanied by potentiating factors, such as the concurrent administration of sulfonamides, may result in this effect. Primaquine should be given with extreme care to patients concomitantly treated with myeloid depressant drugs or who suffer from bone-marrow depression from whatever cause.

Primaquine is an oxidant drug and its administration may cause the conversion of haemoglobin to methaemoglobin, producing cyanosis when the methaemoglobin concentration exceeds 15–20 g per litre of blood, or approximately 10% of the normal haemoglobin level. Methaemoglobin concentrations up to 25% are usually well tolerated. Withdrawal of primaquine will result in the disappearance of symptoms within 24–72 hours.

The lymphocyte proliferative responses to malaria are inhibited by doses of primaquine within the range normally used to treat *P. vivax* infections (*39*). The significance of this finding is not clear

but it has been suggested that primaquine administration should begin only after the acute phase of the disease has passed (*40*).

The haemolytic action of primaquine is increased in subjects with a genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD). Primaquine should therefore be avoided in pregnancy since all fetuses are relatively G6PD-deficient.

Persons with the African variant A of G6PD deficiency may be given the standard therapy for radical treatment of relapsing malaria —i.e., 15 mg daily for 14 days—without individual monitoring as the mild, self-limiting haemolysis that may occur with this dose does not produce any clinical symptoms (*40*). Higher doses, however, require close observation of patients since acute haemolytic crises may occur. Serious haemolysis may also occur when 15 mg daily or even 45 mg weekly are given to individuals with the Mediterranean variant B and Asian variants. Thus, a clear understanding of the prevalence and distribution of variants of G6PD deficiency is required and the risks must be adequately assessed before large-scale administration of primaquine to the residents of the endemic countries where these variants exist is contemplated.

In addition to G6PD deficiency, changes in other enzymes of the pentose-phosphate and associated pathways may also render erythrocytes hypersensitive to haemolysis by primaquine. These enzymes include 6-phosphogluconate dehydrogenase, glutathione synthetase, glutathione reductase, and glutathione peroxidase (*41*). Molecular variants of haemoglobins that are susceptible to oxidant stress, such as Hb Zurich, Hb Bushwick, Hb Torino, and Hb Rush, may also be associated with haemolysis in the presence of primaquine (*42*).

3.2.7 *Tetracycline*

3.2.7.1 *Efficacy*. Tetracycline is an effective but slow blood schizontocide and is therefore never used alone for the therapy of malaria. It is usually administered orally with quinine, a fast-acting blood schizontocide that gives initial control of parasitaemia and symptoms. This combination has been studied in Thailand and found to be highly effective (*43–45*). It has become standard there to administer quinine at a dose of 10 mg/kg of body weight 3 times a day for the first 3 days of a 7-day course of tetracycline. The tetracycline is given at a total daily dose of 1–2 g, divided into 2–4

doses. The Thai antimalaria programme has obtained very high cure rates of falciparum infections with 2 doses each of 500 mg tetracycline daily. Division of the daily dose into 3–4 doses would be technically better because of the short half-life of tetracycline, but this may be impracticable in the field.

Patients unable to take oral medication because of vomiting or cerebral symptoms may be given intravenous quinine until they are able to tolerate oral tetracycline. Tetracycline should not, however, be given to pregnant women or to children below the age of 8 years, except when the risk of withholding the drug outweighs the risk of damage to developing teeth or bones. Such a situation was seen recently in the displaced population at the Thai-Cambodian border, where the highest malaria mortality occurred among pregnant women and small children: quinine alone was not radically curative and mefloquine was not available.

Quinine administration for more than 3 days usually presents serious problems with compliance in outpatients because of its side-effects. Nevertheless, a higher cure rate among inpatients may be obtained in certain instances by combining tetracycline with a longer course of quinine (*46*). Tetracycline administration, at a total daily dose of 1–2 g as above, may begin simultaneously with the quinine or following it. Tetracycline should not be administered parenterally but await the time when the patient is able to take oral medication; parenteral quinine, however, should be maintained during this period if the patient is parasitaemic.

3.2.7.2 *Toxicity*. The most common side-effects of tetracycline administration are gastrointestinal, including epigastric distress, abdominal discomfort, nausea, vomiting, and diarrhoea. These symptoms are usually dose-related and may be alleviated by giving smaller doses more often. Long-term tetracycline administration may result in alteration of the normal intestinal bacterial flora and overgrowth of the bowel with *Candida, Escherichia coli*, or pathogenic staphylococci.

As already mentioned, tetracycline should not generally be used in pregnant women or in children under 8 years of age since it may produce ossification disorders and discoloration of developing teeth (*4*). This effect is most often seen following long-term administration or repeated short courses. Administration to patients with renal dysfunction may result in excessively high serum levels. Large doses,

particularly when given intravenously, may result in hepatotoxicity, especially in pregnant or postpartum women.

3.3 Drug associations and fixed combinations

Associations and combinations of antimalarial drugs may be used for two strategic purposes: (*a*) to enhance activity in the treatment of individual infections, particularly where drug resistance is a problem, and (*b*) in an attempt to delay the appearance of resistance to one or both of the associated drugs when they are to be used widely in a malaria-endemic area. Drug associations may be additive, potentiating, or complementary (*47*).

Additive associations are those in which the combined effect of the constituents equals the sum of their individual activities. These are usually drugs that act on the same stage of the parasite but have different modes of action. The use of chloroquine together with pyrimethamine was such an association. The rationale for this association was to increase the potency of the antimalarial treatment, to use the sporontocidal action of pyrimethamine to affect transmission, and to delay the appearance of resistance to either agent. Unfortunately, this association probably had no impact on the development of resistance; subsequent studies in one rodent model indicated that the combination had little, if any, effect in delaying the appearance of resistance to chloroquine (*48*).

Potentiating combinations are those in which the combined effect of the components clearly exceeds the sum of their individual activities. The components may act at sequential points in a parasite metabolic pathway. Such activity is seen when drugs acting against the enzyme tetrahydrofolate dehydrogenase (dihydrofolate reductase), e.g., pyrimethamine, are used together with drugs inhibiting dihydropteroate synthase, e.g., the sulfonamides and sulfones.

It is important that the components of additive or potentiating combinations have similar durations of action and that they are given in optimal proportions.

Complementary associations may act against different stages in the life-cycle of the parasite. An example is the use of primaquine and chloroquine to produce radical cure of *P. vivax* infections. Primaquine acts against the latent liver forms, or hypnozoites, of this parasite while chloroquine eliminates the asexual blood stages. Drug action may also be complementary in terms of speed and efficacy, as with combinations of quinine and tetracycline. The use of

mefloquine following initiation of treatment with quinine was also suggested for this reason (*49*), but recent studies indicate that extreme care must be taken when using mefloquine to treat patients who have received cardioactive drugs such as quinine (see section 3.2.5.4).

3.3.1 *Antimetabolites of the folate pathway*

Pyrimethamine, trimethoprim, and cycloguanil and chlorcycloguanil (the active metabolites of proguanil and chlorproguanil) inhibit tetrahydrofolate dehydrogenase, whereas sulfonamides and sulfones inhibit dihydropteroate synthase. These enzymes control successive steps in the parasite's folic acid cycle and, when used together, potentiate each other. Pyrimethamine, proguanil, and chlorproguanil are nowadays seldom used alone for treatment but are given together with a sulfonamide or sulfone with the appropriate pharmacokinetic properties; these combinations are discussed below.

3.3.1.1 *Sulfadoxine/pyrimethamine.* The combination of sulfadoxine with pyrimethamine has been a successful operational antimalarial drug in areas with highly developed resistance to chloroquine. However, resistance to this combination also has now become well established in several south-east Asian countries (*44, 45*) and has been reported from Africa (*50*).

Sulfadoxine/pyrimethamine is usually given for *P. falciparum* infections to adults as a single dose (usually in 3 tablets) of 1500 mg sulfadoxine and 75 mg pyrimethamine. Higher doses are not recommended because of potential pyrimethamine toxicity, and lower doses, if used on a large scale, may select for resistance. The combination is not recommended for prophylaxis owing to the risk of severe cutaneous skin reactions (*51*) (see also section 3.2.5.3).

3.3.1.2 *Other combinations of tetrahydrofolate dehydrogenase inhibitors with sulfonamides or sulfones.* The toxic risks of and the extension of resistance to sulfadoxine/pyrimethamine have stimulated interest in other combinations with the same mode of action, in the hope that their use would be safer and effective. Particularly, hypersensitivity reactions are observed with sulfa drugs that have a high degree of protein-binding and long half-lives. Thus,

a short-acting sulfa drug with less tubular reabsorption and low protein-binding might offer distinct advantages (*51*).

Sulfalene/pyrimethamine: this combination (*52, 53*) has been used in some malaria control programmes to treat chloroquine-resistant *P. falciparum* infections, but there is insufficient experience with it to tell whether it is significantly different from the sulfadoxine/pyrimethamine combination in selecting for resistance or in causing adverse reactions to the sulfonamide component.

Sulfones/biguanides: Studies in Kenya have shown that chlorcycloguanil (the major metabolite of chlorproguanil) and dapsone in combination are strongly synergistic *in vitro* against local *P. falciparum* isolates (*54*). *In vivo*, a single dose of chlorproguanil combined with dapsone, 1.2 mg of each compound per kg of body weight, produces parasite clearance comparable to that following the administration of sulfadoxine/pyrimethamine. Both combinations are highly effective in clearing parasitaemia during the first 7 days after administration although recrudescences occur later (*54*). Whether the very favourable pharmacokinetic profile and demonstrated schizontocidal effect of the chlorproguanil/dapsone combination are sufficiently advantageous to support wider operational use needs further study.

3.3.1.3 *Toxicity of preparations containing sulfonamides and sulfones.* The most frequent and serious side-effects associated with sulfonamides involve the skin and mucous membranes. They range from mild, self-limiting lesions to vesicular exanthemata and bullous, exfoliative reactions including the Stevens-Johnson syndrome and toxic epidermal necrolysis, both of which may be fatal in 10–20% of cases (see also section 3.2.5.3). Such reactions are not necessarily dose-related and are not predictable by a "classical" history of sulfonamide allergy.

The major adverse reactions to sulfones are haematological and are reported even in association with relatively small doses. Methaemoglobinaemia may be observed with dapsone doses routinely used for malaria prophylaxis and may be potentiated by concomitant administration of other antimalarials, such as chloroquine and primaquine. Severe haemolytic anaemia may also be associated with dapsone. For example, when 25 mg of dapsone were given daily and chloroquine and primaquine weekly to United States soldiers in Viet Nam, severe haemolysis occurred in blacks who were G6PD-deficient (*55*). Haemolysis also occurred in this

group, but to a lesser extent, when primaquine was given alone, suggesting a dapsone–primaquine synergy in the pathogenesis of this condition.

The most serious side-effect related to dapsone is agranulocytosis. Sixteen cases of agranulocytosis, including 8 deaths, occurred in United States soldiers in Viet Nam using a combination of dapsone/chloroquine/primaquine for prophylaxis. It was estimated that around 200 000 soldiers were using this regimen at that time, giving a frequency of agranulocytosis of 1 in 12 500 (*55*). Three nonfatal cases of agranulocytosis, which were considered to have been caused by dapsone, occurred in the Australian and New Zealand forces in Viet Nam, who were using 200 mg proguanil and 25 mg dapsone daily (*56*). More recent studies have shown agranulocytosis to occur in 1 in 2000 persons using 200 mg dapsone weekly (*57*).

Serious cutaneous reactions (*58, 59*) and pulmonary disorders (*60*) have been reported in Australia and the United Kingdom following the weekly use of pyrimethamine/dapsone for prophylaxis.

3.3.2 *Combinations of artemisinin and its derivatives with other drugs*

In view of the relatively high recrudescence rates observed when artemisinin and its derivatives, particularly the parent compound, have been used clinically to treat *P. falciparum* infections (see section 8.3), Chinese clinicians have carried out comparative studies on their combination with other standard antimalarials.

Cure rates of 100% without recrudescences were reported in symptomatic falciparum malaria patients receiving a single intramuscular dose of 500 mg of artemisinin plus the oral administration of 1 g sulfadimethoxine, 70 mg pyrimethamine and 30 mg primaquine base (*61*). Patients receiving chloroquine alone (total oral dose of 25 mg base per kg of body weight over 3 days), artemisinin alone (500 mg artemisinin given intramuscularly on each of 2 days), or sulfadimethoxine, pyrimethamine and primaquine (oral dose of, respectively, 1 g + 70 mg + 30 mg base) showed recrudescence rates of 41% with chloroquine, 90% with artemisinin, and 67% with the triple combination. Recrudescences were not observed when a single dose of 300 mg artemether was combined with oral administration of 1 g sulfadoxine, 70 mg pyrimethamine, and 30 mg primaquine base for the treatment of chloroquine-resistant falciparum malaria (*62*).

In another study, four regimens were compared in a total of 80 patients with falciparum malaria: (1) mefloquine plus sulfadoxine/pyrimethamine, (2) mefloquine plus artemisinin, (3) artemisinin alone, and (4) mefloquine plus sulfadoxine/pyrimethamine plus artemisinin (*63*). Fever clearance was fastest following the administration of combination 4, while parasite clearance was fastest with treatment using artemisinin alone. No recrudescences were seen with regimens 1, 2 and 4, but recrudescences were observed in 41% of the patients receiving artemisinin alone.

Since parasite clearance was slower following treatment with the combination of mefloquine and artemisinin than following treatment with artemisinin alone, it was suggested that there might be antagonism between the two drugs (*64*). This is in marked contrast to *in vivo* studies with *P. berghei* and *in vitro* studies with *P. falciparum*, both of which showed these drugs to potentiate each other; but antagonism was observed between artemisinin and the antifolates pyrimethamine and sulfadoxine in both these laboratory models (*65*). However, the quadruple combination of mefloquine, sulfadoxine, pyrimethamine, and artemisinin produced the fastest defervescence and also cleared parasitaemia more rapidly than mefloquine plus artemisinin (*63*).

The rationale for the use of such combinations has been questioned because the high recrudescence rates observed when artemisinin has been used alone may be due merely to failure to use the correct dosage regimen (*64*). In fact, only limited dose-finding studies have been carried out with any of the formulations of artemisinin or its derivatives, and the regimens used in the clinic have not been based on pharmacokinetic principles as adequate methods for determining blood levels in humans have not been available. It is therefore too early either to draw detailed conclusions from the limited clinical studies or to embark on further combination studies in the clinic.

3.4 Antimalarial chemotherapy of pregnant women

Falciparum malaria during pregnancy poses a threat to the life of the mother and the fetus or may lead to severe anaemia and fetal growth retardation. Either rapid treatment of acute infection or effective prophylaxis is therefore essential to avoid severe manifestations and complications. Chloroquine and quinine have

proved to be safe when used in normal therapeutic doses during pregnancy, and chloroquine may also be used prophylactically where it is effective. Regimens containing pyrimethamine and tetracyclines are, however, contraindicated during both pregnancy and lactation.

The small number of antimalarial drugs that can be used during pregnancy has led recently to the study of the efficacy and safety of mefloquine, both for treatment and prophylaxis of this special group at risk from malaria. A double-blind randomized controlled trial was conducted between 1983 and 1989 on the treatment of women in Chantaburi, Thailand (T. Harinasuta & D. Bunnag, personal communication). Mefloquine was administered in 2 doses of 500 mg each over 8 hours and compared with a 7-day course of 600 mg of quinine sulfate given orally every 8 hours for 7 days.

Uterine contractions during antimalarial treatment occurred in 18% of the patients receiving mefloquine and in 25% of those given quinine. However, these contractions resulted in premature labour in only 1% of the mefloquine patients and in 5% of the quinine patients. Fetal distress during the treatment was seen in 2% of the mefloquine patients and in 4% of the quinine patients. There was one abortion in each drug group, but these occurred 21 and 37 days following drug administration and were considered to be unrelated to treatment. No stillbirths occurred following either drug treatment. There were no significant differences in the frequency of uterine contractions, premature labour, or fetal distress between the two groups of patients.

Parasite clearance occurred in all 91 infections treated with quinine and in 86 of 87 infections treated with mefloquine. Follow-up of these patients for 21 days after parasite clearance detected 13 infections due to *P. falciparum* in the quinine group and 2 infections with the same parasite in the mefloquine group, giving 21-day cure rates of 86% and 97% respectively, assuming reinfection did not occur. However, reinfection cannot be excluded since this study was conducted in an endemic area; this is particularly relevant in interpreting the results from the quinine group, which received a drug with a plasma half-life of 6–8 hours. Five *P. vivax* infections were noted during follow-up in the mefloquine group and 16 in the quinine group. It was concluded that the therapeutic use of mefloquine during pregnancy was both safe and effective.

Its use in the first trimester, however, should be kept to a minimum since the number of patients at this stage of pregnancy in

the above study was very small. There is also evidence in rats and rabbits of teratogenicity and embryotoxicity when mefloquine is given at high doses. Thus, during the first 12–14 weeks of pregnancy, mefloquine should be administered for treatment only when the benefit to the mother outweighs the risk to the fetus.

Two clinical trials of mefloquine prophylaxis during pregnancy are being undertaken but have not yet progressed sufficiently for clear findings to emerge. The Scientific Group considers that, until more definite results have been obtained, mefloquine prophylaxis should be avoided during pregnancy.

3.5 Administration of antimalarials to infants and children

The administration of a bitter drug like chloroquine to young children is always difficult, and there is no evidence that syrups are easier to administer than tablets crushed and mixed with water. Very often, force is used (including closing the child's nostrils to make it open its mouth), which entails a risk of aspiration. Even with such strenuous efforts, an uncertain quantity of the drug may be spat out, leading to underdosage—or even to overdosage if repeated attempts are made. In addition, chloroquine itself is a powerful emetic.

To counterbalance these rather pessimistic remarks, the following example is offered of a simple yet effective means of administering antimalarials to children. At a health centre in Beira, Mozambique, approximately 20–30 children are seen each day presenting with fever as the main symptom. These children are identified by the nurse, who takes their temperature and weight. Paracetamol and liquids (for children needing oral rehydration) are administered immediately, and the skin is cooled with water and by fanning. After that, a blood film is taken. Within 1½–2 hours, the result of the blood film is usually available. The child is by then usually fit to take oral chloroquine if that is needed.

For many reasons, the parenteral administration of chloroquine is generally not satisfactory, but suppository formulations may provide a suitable alternative. The bioavailability of chloroquine after rectal administration should be considered a very important research topic. If the results are satisfactory, suppositories might prove a highly appropriate form of administration for young children.

3.6 Accessory treatment

3.6.1 *Rehydration*

Especially in hot climates, febrile patients with malaria may become dehydrated and children, whose tolerance of fasting is limited, may become hypoglycaemic. Community education programmes should therefore encourage the oral rehydration of febrile patients. Glucose supplements, as in oral rehydration formulas for the control of diarrhoea, might reduce the frequency of hypoglycaemia.

3.6.2 *Antipyretics*

Bed rest and lowering of body temperature may reduce vomiting and allow patients to be treated orally. Physical methods, such as removal of clothes, fanning and tepid-sponging, are the most reliable. A variety of antipyretic drugs have been used in the management of malaria patients. Paracetamol is preferred to aspirin, which has been associated with an increased risk of Reye syndrome in children and with gastric bleeding and fetal toxicity when used in pregnancy. Corticosteroids should not be used as they increase and prolong parasitaemia. Injectable antipyretics, such as metamizole sodium (dipyrone), are widely used in tropical countries but are unacceptable because of the risk of agranulocytosis. Paracetamol can be given by mouth or suppository; crushed tablets can be administered via nasogastric tube.

3.6.3 *Anaemia*

Chronic and progressive anaemia, caused by repeated attacks of malarial haemolysis, other infections, congenital haemoglobin abnormalities, and nutritional deficiencies, is a major problem associated with the treatment of malaria, especially in children and pregnant women. Haematinics (such as iron and folic acid), treatment of other infections (such as hookworm), and in some cases blood transfusion may be needed.

3.7 Hazards of the casual, undocumented use of antimalarials

When treatment is given to a patient with malaria, great care should be taken to find out whether or not antimalarial or other drugs have already been administered.

A typical sequence of events for a patient with malaria is often as follows. After feeling poorly for a few days, the patient has a particularly bad night, experiencing severe symptoms of malaria. He goes the next morning to a private source or to a health post for treatment, possibly with chloroquine or mefloquine. He may then feel better for the rest of the morning but then ill again in the afternoon or evening, possibly vomiting from the effect of the drug he has received and absorbed. He is likely to go next to a hospital, doubting the competence of the first prescriber and considering that the drug he received earlier did him no good. Generally where hospital staff are overworked, detailed histories are not taken. The patient, not surprisingly, is found to have malaria parasites in his blood film, and he will often be given the standard treatment for serious malaria. If this involves a parenteral loading dose of quinine, it may result in a high quinine peak level at precisely the same time that his earlier oral dose of chloroquine or mefloquine is reaching its peak. As the cardiac pharmacodynamics of these drugs are similar, serious complications could result.

A similar situation may apply to the routine administration of parenteral chloroquine, as has been noted in section 1.4. It was found in the course of a survey in Nigeria that 50% of children attending an outpatient clinic for malaria treatment already had "therapeutic" blood levels of chloroquine at the time they were seen (T. Ogbuokiri, personal communication).

3.8 The need for simple, operational tests for antimalarials in blood and urine

Self-medication for malaria is already widespread and is increasing. It is therefore of vital importance to develop simple and cheap methods for the detection of antimalarials in blood and urine. In addition, an increasing array of clinical and epidemiological situations has evolved in recent years in which the ability to assess for the presence of malarial drugs in body fluids, especially urine, is required. It is necessary, for example, to be able:

—to determine prior drug use in the case of suspected therapy failure in *P. falciparum* infection;
—to determine the presence of antimalarial drugs prior to therapy in order to assess the risk of drug interactions or to decide if a change of dosage is required;

—to exclude patients who have already been treated from drug efficacy studies;
—to assess compliance with prescribed or reported drug use, e.g., with chemoprophylaxis.

The Dill-Glazko urine test for 4-aminoquinolines has been widely used, but it has now been shown to be highly insensitive and unreliable (*66, 67*). Recently, assays have been developed—principally for 4-aminoquinolines—that are highly sensitive and specific and that can be employed simply and reliably under basic field conditions (*68*). They are of two types: colorimetric assays (*69–71*) and enzyme-linked immunoassays employing specific monoclonal or polyclonal antibodies (*72, 73*). Several of these assays are semi-quantitative, and estimates from urine correlate well with whole-blood drug concentrations. In addition, techniques have been developed whereby drug estimations can be made at a well equipped laboratory by more sophisticated techniques, such as thin-layer chromatography, from finger-stick blood samples taken in the field and spotted on to filter-paper (*74–76*).

The tests on urine for which there is adequate standardization and experience of use in field settings are listed in Table 1. The Saker-Solomons test for chloroquine is of particular importance since it has the characteristics of a valuable general screening test for urine to determine with great sensitivity if an individual has recently ingested the drug. The Haskins MMII, the high-performance thin-layer chromatography, and the ELISA methods can detect very low amounts of chloroquine and its metabolites.

Development of comparable analytical methods for other malaria drugs is important. In particular, the deployment of mefloquine and quinine could be rationalized if tests were available to assess drug use quickly and to measure drug concentrations in field and clinical settings.

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Table 1. Characteristics of field-adapted assays for chloroquine in urine[a]

Method	Detection limit (μg/ml)	Between-assay coefficient of variation (%)	Selectivity (specificity)	Compounds detected	References
Wilson-Edeson	4	Not applicable (qualitative)	Fair	Chloroquine, metabolites, quinine	69, 77, 78
Haskins	2	Not applicable (qualitative)	Fair	Chloroquine, metabolites, quinine, proguanil	69, 77, 79
Dill-Glazko	40–80 (variable)	Not applicable (qualitative)	Fair	Chloroquine, amodiaquine, metabolites, quinine	66,[b] 67,[b] 69, 77, 80
Bromthymol blue	3	5–10	Fair	Chloroquine, metabolites, quinine, proguanil	69
Haskins MMII (MMI)	1 (0.3)	5–10	Fair	Chloroquine, metabolites, quinine, proguanil	70, 81[b]
Saker-Solomons CQI	1	Not applicable (qualitative)	Fair	Chloroquine, metabolites, quinine, proguanil	71
Saker-Solomons CQII	2	5–10	Fair	Chloroquine, metabolites, quinine, proguanil	71
HPTLC-FQ[c]	0.25	Not applicable (semi-quantitative)	Excellent	Specific for chloroquine, desethylchloroquine	82[b]
HPTLC-FQ-SLM[d]	0.25	10–15	Excellent	Specific for chloroquine, desethylchloroquine	75
HPTLC-F[e]	0.025	Not applicable (semi-quantitative)	Excellent	Specific for chloroquine, desethylchloroquine	74
HPTLC-F-SLM[f]	0.025	10	Excellent	Specific for chloroquine, desethylchloroquine	75
ELISA-A	0.001	Not stated	Good	Chloroquine, amodiaquine, metabolites	73[b]
ELISA-B	0.0003	5–10	Excellent	Specific for chloroquine	72

[a] Reproduced from reference *68*, by permission.
[b] Includes description of field application.
[c] High-performance thin-layer chromatography (HPTLC) with visual detection of background fluorescence quenching by analyte spots under ultraviolet light (254 nm).
[d] HPTLC with detection by spot luminance meter of background fluorescence quenching by analyte spots under ultraviolet light (254 nm).
[e] HPTLC with visual detection of visible fluorescence under ultraviolet light (254 nm).
[f] HPTLC with detection by spot luminance meter of visible fluorescence under ultraviolet light (254 nm).

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4. THE MANAGEMENT AND TREATMENT OF SEVERE FALCIPARUM MALARIA

Severe, life-threatening malaria is nearly always caused by *P. falciparum*. However, vivax malaria can be fatal in patients who suffer traumatic or spontaneous rupture of the spleen and in those who develop severe anaemia, especially debilitated and malnourished patients. Transfusion malaria caused by *P. malariae* and *P. vivax* may also occasionally prove fatal in immunocompromised patients. Only severe falciparum malaria will be considered in this section.

4.1 Characteristics of severe falciparum malaria

Diagnosis or suspicion of severe falciparum malaria calls for either immediate and special treatment, including parenteral chemotherapy, or referral to a level of the health service where this can be accomplished. The following outline is intended to help clinicians recognize severe disease and to indicate the features of malaria that should be looked for and systematically recorded in any study of severe falciparum malaria.

The following indicate a diagnosis of severe falciparum malaria in a patient with *P. falciparum* asexual parasitaemia.

(*a*) *Unrousable coma:* not attributable to any other cause such as bacterial meningitis or locally prevalent viral encephalitides (*1, 2*).

(*b*) *Severe normocytic anaemia:* erythrocyte volume fraction less than 0.15 (haematocrit <15%), haemoglobin less than 50 g/l, associated with parasitaemia more than 100 000/μl. If anaemia is hypochromic and/or microcytic, iron deficiency must be excluded.

(*c*) *Renal failure:* urine output less than 400 ml per 24 hours in adults or 12 ml/kg of body weight per 24 hours in children; serum creatinine more than 265 μmol/l (>3.0 mg/dl), failing to improve after rehydration.

(*d*) *Pulmonary oedema or adult respiratory distress syndrome.*

(*e*) *Hypoglycaemia:* whole blood glucose less than 2.2 mmol/l (<40 mg/dl).

(*f*) *Circulatory collapse or shock* from any cause, including dehydration: systolic blood pressure less than 50 mmHg in children aged 1–5 years or less than 70 mmHg in adults, with cold clammy skin or core–skin temperature difference more than 10 °C.

(*g*) *Spontaneous bleeding* from gums, nose, or gastrointestinal tract and/or laboratory evidence of disseminated intravascular coagulation.

(*h*) *Repeated generalized convulsions:* more than 2 within 24 hours despite cooling.

(*i*) *Acidaemia:* arterial pH less than 7.25; or *acidosis:* plasma bicarbonate less than 15 mmol/l.

(*j*) *Macroscopic haemoglobinuria:* if definitely associated with acute malaria infection and not merely the result of oxidant anti-malarial drugs in a patient with G6PD deficiency.

(*k*) *Postmortem confirmation of diagnosis:* in fatal cases, the diagnosis is confirmed by finding venules or capillaries in the cerebral grey matter packed with erythrocytes containing mature trophozoites and schizonts of *P. falciparum*.

Other manifestations of severe malaria which do not in themselves define the condition in all geographical areas and age groups include the following:

—Impairment of consciousness, but less marked than unrousable coma.
—Prostration or weakness, so that the patient cannot sit up or walk, with no obvious neurological explanation.
—Hyperparasitaemia: the relationship between parasitaemia and severity of illness varies in different populations and age groups

but in general very high parasite densities are associated with increased risk of severe disease.

—Jaundice: detected clinically or serum bilirubin more than 50 μmol/l (> 3.0 mg/dl).

—Hyperpyrexia: rectal temperature more than 40 °C in adults and children.

4.2 Vomiting and the need for initial parenteral chemotherapy

Vomiting and inability to swallow oral drugs have been taken as a criterion of severe disease as the patients may require parenteral treatment. However, many such patients, especially children, will eventually be able to swallow and retain tablets if they are laid quietly in bed, cooled, encouraged to take oral rehydration fluid, and left for 30 to 60 minutes before a further attempt is made to administer the antimalarial drug. Patients who vomit persistently may require treatment by injection, nasogastric tube or suppository. If these patients have no other features of severe malaria, they may require only one or two doses of parenteral treatment and have an excellent prognosis. Thus vomiting and the need for initial parenteral administration of drugs should not be considered a true criterion of severe malaria.

4.3 Principles of management of severe falciparum malaria

4.3.1 *General principles* (*3*)

A suspicion of severe falciparum malaria is of the utmost importance. Attempts should be made to confirm the diagnosis but, failing that, clinical suspicion should prompt antimalarial therapy even if parasites are not found in the blood film. Severe falciparum malaria is a medical emergency demanding the highest level of treatment available, preferably in an intensive care unit. A rapid initial clinical assessment is useful, followed by complete clinical examination after treatment has been started. Temperature should be measured, preferably rectally, and the patient cooled if necessary. Hypoglycaemia must be excluded in patients with any impairment of consciousness by rapid checking of blood glucose using an indicator stick or by a therapeutic trial of intravenous glucose. Useful laboratory tests include malaria parasite, platelet, and white cell counts as well as measurements of haematocrit or haemoglobin,

serum electrolytes, and urea or creatinine. In patients with cerebral malaria and in those who have had a convulsion, prophylactic anticonvulsants should be considered (*4*).

The priorities in the chemotherapy of severe and of uncomplicated malaria are clearly different. The use of single-dose regimens to ensure compliance, the prevention of late recrudescences, and the destruction of gametocytes to prevent further transmission are of minor importance in severe malaria. Unpleasant side-effects such as cinchonism or pruritus, which may be important in the treatment of uncomplicated malaria, are acceptable in the treatment of a life-threatening infection and should not limit dosage.

The principles of the management of severe falciparum malaria are summarized in Table 2.

Table 2. Principles of management of severe falciparum malaria

- If early suspicion of severe malaria, transfer patient to highest level of care available. Make initial clinical assessment.
- Give early antimalarial chemotherapy, using optimal doses of an appropriate agent administered by parenteral route.
- Prevent complications (e.g., convulsions, hypoglycaemia, hyperpyrexia), or ensure early detection and treatment.
- Correct fluid, electrolyte, and acid–base balance.
- Give proper nursing care (e.g., of unconscious patients).
- Avoid harmful ancillary treatments (e.g., corticosteroids).

4.3.2 *Principles of early treatment*

In a study conducted in eastern Thailand of patients with severe falciparum malaria, almost all deaths occurred during the first 96 hours after admission to hospital and the start of quinine treatment. There was a highly significant correlation between delay in starting quinine treatment and mortality (*1*). To have any impact on mortality, chemotherapy must be started as quickly as possible, using a rapidly acting schizontocidal drug to which the parasites are likely to be sensitive. Only intravenous administration ensures bioavailability of the drug under all clinical conditions, which may include vomiting, gastrointestinal malabsorption, and shock. From a theoretical point of view, the ideal regimen would be one that

achieves blood concentrations above the *in vitro* or *in vivo* minimal inhibitory concentration (MIC) as quickly as possible but without dangerous side-effects. Unfortunately, few data are available to judge the clinical value of this approach or the validity of using the MIC as a target blood concentration (*5, 6*).

A loading dose has been widely used by clinical pharmacologists to achieve rapidly therapeutic blood levels of a drug. In the case of antimalarial drugs, which have a relatively narrow therapeutic ratio, pharmacokinetic modelling has allowed the development of regimens which produce a rapid increase in blood concentration to plateau levels around the *in vitro* MIC, without exceeding levels that would result in cardiovascular and other toxicity (*5*). Parasite clearance times were significantly reduced in a preliminary study in which a loading dose of quinine was used (*5*). However, larger-scale studies are needed to assess the clinical efficacy of using such a loading dose and to compare higher maintenance doses of quinine with conventional lower-dose regimens without a loading dose. Theoretically, the rapid killing of parasites might produce a Jarisch-Herxheimer reaction in the patient. This has not been observed in studies in Thailand (D.A. Warrell, personal communication), but a recent study of quinine treatment of children in Zaire described clinical deterioration, fever, seizures, and haemolysis associated with a sudden lysis of parasitaemia on the second day of chemotherapy (*7*). A similar phenomenon was observed in Malawian children (M.E. Molyneux, personal communication). These events deserve further study, particularly to combine intensive clinical observations with the measurement of inflammatory mediators. Adequate blood concentrations of antimalarial drug should be sustained for long enough to ensure clearance of asexual parasitaemia and preferably to prevent recrudescence. Chongsuphajaisiddhi et al. (*6*) demonstrated that if the plasma quinine concentrations in children were allowed to fall below the *in vitro* MIC during the first 5–7 days of treatment, recrudescences were more likely to occur.

As has already been mentioned, previous treatment with antimalarial drugs is prevalent in many parts of the world among patients presenting with severe malaria (*1, 8*). Every attempt should therefore be made to discover by questioning or urine testing whether this is the case, since a loading dose of quinine or quinidine might produce dangerously high plasma concentrations if either of these drugs or mefloquine has been taken in the previous 12–24 hours. A past history of cardiac arrhythmias, heart disease, or

hypersensitivity to antimalarial drugs should also be determined since the cinchona alkaloids are cardioactive. There may also be clinically significant interactions between digoxin and quinine, and between mefloquine and beta-blockers.

Whenever possible, the dosage of antimalarial drugs for use in severe malaria should be calculated according to body weight but it is uncertain whether the standard recommendations should be altered for extremes of weight, such as obesity or malnutrition. Length/height or age nomograms may be used where it is impossible to weigh the patient. Calculation of dose is less important in the treatment of adults within the normal range of body weights, for whom a standard adult dose can be used.

The response to chemotherapy must be frequently monitored by clinical examination of the patient, by recording temperature, pulse and blood pressure, and by repeated parasite counts. As soon as the patient is able to swallow tablets, the full course of treatment should be completed orally.

(See recommendation 9.4.1.)

4.4 Antimalarial drugs

4.4.1 *Quinine*

Quinine is the drug of choice for the treatment of severe chloroquine-resistant falciparum malaria, for severe infections which have "broken through" chloroquine prophylaxis, and for infections whose origin is not known. Clinicians may even decide to use quinine in all severe infections because of the widespread occurrence of chloroquine resistance in *P. falciparum*.

(*a*) *Intravenous administration.* Since rapid intravenous "push" or bolus injections of quinine can cause severe or even fatal cardiovascular toxicity, the drug should never be given in this way (*9*). Surprisingly, intravenous injection over 10 or 20 minutes is still advocated in some well known textbooks. Ideally, quinine should be given by slow, constant, controlled-rate intravenous infusion diluted in isotonic fluid (5–10 ml per kg of body weight, depending on the patient's overall fluid balance).

Rapid but safe increases in blood levels of quinine to plateau around the MIC can be achieved by the use of a loading dose (*5, 10*). This is at least theoretically desirable in the treatment of severe

falciparum malaria. The loading dose should not be used if the patient has received quinine, quinidine, or mefloquine during the previous 12–24 hours. Although there is no clinical evidence that pretreatment with chloroquine increases the risk of toxicity of a loading dose of quinine, there is theoretical concern that this might be the case and the clinician should be aware of it. Where nursing care and equipment allow, the ideal regimen is probably to start with a loading dose of 7 mg quinine dihydrochloride per kg of body weight given over 30 minutes by constant-rate intravenous infusion, followed immediately by a dose of 10 mg/kg given over the next 4 hours (*10*). Alternatively, a loading dose of 20 mg/kg can be given by constant-rate intravenous infusion over 4 hours (*5, 11*). A maintenance dose of 10 mg quinine dihydrochloride/kg can be safely infused over 4 hours every 8 hours until the patient is able to swallow tablets and to complete a 7-day course of quinine. It is likely that the maintenance dose could be infused over a shorter period. However, in Malawian children with cerebral malaria, the plasma insulin concentration and insulin–glucose ratios increased significantly when a dose of 10 mg/kg was infused over 1 hour; this was not observed when the drug was infused over 3 hours (T.E. Taylor & M.E. Molyneux, personal communication).

Misunderstandings have arisen because the principle of using a loading dose has been confused with the absolute doses required in different geographical areas. Loading and maintenance doses described above were found to be necessary in Thailand where the *in vitro* MIC of quinine for local strains of *P. falciparum* was around 10 mg/l. It is possible that in areas such as Kenya, where *P. falciparum* appears to be more sensitive to quinine, a loading dose of 10 mg/kg and maintenance doses of 5 mg/kg, given at 12-hour intervals, might produce adequate plasma concentrations.

(See recommendation 9.4.1.)

If, after 48 hours of parenteral treatment, the patient is still unable to take oral treatment or if there is evidence of significant renal or hepatic impairment, the maintenance dose should be reduced by half. However, the loading dose of quinine should not be reduced in patients with renal and hepatic impairment. If rapid monitoring of plasma quinine concentrations is possible, the dose should be reduced at any stage if the plasma concentration exceeds 15 mg/litre.

Plasma concentrations of quinine above 5 mg/l may produce cinchonism (see section 3.2.3.2). Quinine may also cause blind-

ness, deafness, hypotension, electrocardiographic abnormalities, and central nervous system depression at concentrations above 20 mg/l. Malaria patients with plasma concentrations of quinine in the range 15–25 mg/l, however, show far less cardiovascular and neurological toxicity than would be expected in comparison with people who take overdoses of quinine. This may be explained by increased binding of the drug to acute-phase proteins. Quinidine (see section 4.4.6) causes greater prolongation of the QT_c interval and QRS complex than quinine (*12*) but this is rarely associated with dysrhythmia or hypotension unless the drugs are given too rapidly (*5, 9, 13*). Hypoglycaemia, caused by hyperinsulinaemia, is the commonest important side-effect of quinine or quinidine administration (*5, 21*). This could usually be prevented in Malawian children by continuous infusion of 5% dextrose (80 ml/kg over 24 hours) (*11*).

Although high doses of quinine may stimulate the pregnant uterus and have been used to induce abortion, normal therapeutic doses can be used with confidence during the initial treatment of pregnant women, even in the third trimester (*14, 15*). Thai women who were more than 30 weeks pregnant and had severe falciparum malaria showed no evidence of uterine stimulation or fetal distress during the initial intravenous infusion of quinine (*15*). However, further studies are needed to monitor the uterus and the fetus in women who require prolonged parenteral treatment with quinine. Pregnant women are particularly vulnerable to quinine-induced hyperinsulinaemic hypoglycaemia and hypoglycaemia unrelated to quinine administration (see section 4.5.3). Monitoring of blood glucose by repeated finger-prick testing with indicator sticks is therefore desirable in pregnant women with malaria.

(*b*) *Intramuscular administration.* When intravenous infusion of quinine is not possible, quinine dihydrochloride may be given by deep intramuscular injection—for example, in the anterior thigh muscle (*16–18*). More dilute solutions than the standard intravenous preparation of 300 mg/ml quinine dihydrochloride may be less painful, especially if adjusted to a neutral pH (N.J. White, personal communication). However, the dosage, including the loading dose, is the same as with intravenous formulations of quinine. Injections can be given at multiple sites to reduce the volume of a single inoculum.

Quinine has been widely used by the intramuscular route but in some cases this has led to reports of formidable side-effects including

muscle necrosis, abscess formation, nerve damage, and even paraplegia. Such reactions may be related to the use of preparations formulated in urethane or other irritant substances. However, quinine dihydrochloride appears to have been well tolerated, the bioavailability of the drug given intramuscularly being adequate even in severely ill children (M.E. Molyneux & T.E. Taylor, N.J. White, personal communications). There are, however, individual variations in the speed of absorption in healthy subjects and important differences in the speed of elimination of different preparations of this quinine salt.

It is particularly important to prevent and recognize quinine-induced hypoglycaemia in patients, especially children, receiving intramuscular quinine. Such patients may not have an intravenous infusion line in place to allow prompt infusion of glucose.

(*c*) *Other routes*. Quinine should not be given by subcutaneous injection as this causes skin necrosis. There are no published data on the use of quinine suppositories, but these might be of great value at peripheral levels of the health service.

4.4.2 *Mefloquine*

Mefloquine is effective against some quinine-resistant strains of *P. falciparum*. Unfortunately, it is too irritant to be given by injection. Absorption of a mefloquine suspension given by nasogastric tube to patients with cerebral malaria was rapid but unreliable in very sick patients in a study in Thailand (*19*).

4.4.3 *Chloroquine*

Chloroquine remains useful in those dwindling areas of the world in which *P. falciparum* is still susceptible to this drug, because it is less toxic than quinine and may be more rapidly effective. There have been few attempts to compare the efficacy of chloroquine and quinine in patients with chloroquine-sensitive falciparum malaria or to compare the tolerance of patients to these two drugs. However, in a small study of patients with parasitaemias in excess of 500 000/ml, Wilson & Edeson (*20*) found that fewer deaths occurred following chloroquine use than with quinine. Advantages of chloroquine over quinine are that it does not cause hypoglycaemia (*21*), has not been associated with intravascular haemolysis or blackwater fever, and does not stimulate the pregnant uterus.

Cardiovascular toxicity has been associated with transiently high blood concentrations of chloroquine following rapid intravenous administration or the use of relatively large intramuscular or subcutaneous doses of 5–10 mg base/kg body weight (*22*). Very high plasma concentrations (>1000 mg/ml), as may be reached with some parenteral administration, may cause vasodilation, hypotension, cardiotoxicity, and even death. The toxic effects can be prevented by intravenous infusion at a slow controlled rate, e.g., 10 mg base/kg of body weight diluted in isotonic fluid given over 8 hours, followed immediately by 15 mg base/kg given over the next 24 hours, or 5 consecutive infusions of 5 mg base/kg, each given over 6 hours. The total dose in each case is 25 mg base/kg. Severe chronic toxicity can be treated with diazepam, isoprenaline, and ventilatory support in an intensive care unit (*23*).

When it is not possible to give an intravenous infusion, chloroquine may be given by subcutaneous or intramuscular injection or by nasogastric tube—or by suppository, if this formulation is developed. (These routes of administration may also be recommended for initiating treatment in patients with uncomplicated disease who vomit repeatedly and cannot swallow or retain oral treatment.) Intramuscular or subcutaneous chloroquine is rapidly absorbed, even in severely ill patients, and so the doses should be small (2.5 or 3.5 mg base/kg body weight) and given at relatively frequent intervals (*24*, *25*). In a study of 16 Gambian children with malaria requiring parenteral treatment, chloroquine given intramuscularly or subcutaneously in a dose of 3.5 mg base/kg at 6-hourly intervals was safe and effective (*26*). Most of the children required only two parenteral doses before oral treatment with chloroquine was possible; in the remainder, peak blood chloroquine concentrations after the third and subsequent doses ranged from 560 to 2500 mg/ml, but there was no evidence of cardiotoxicity (N.J. White, personal communication). White et al. (*25*) predict that chloroquine given at a dose of 2.5 mg/kg at 4-hour intervals by intramuscular or subcutaneous injection would be an acceptable alternative, but this regimen has not been formally studied in patients.

Fatal circulatory collapse following intravenous or intramuscular chloroquine, especially in African children, led the previous WHO Scientific Group on the Chemotherapy of Malaria to suggest that parenteral chloroquine should never be used (*27*). This was prompted by fears that toxic levels of chloroquine might rapidly be

attained in patients, many of whom had been pretreated with the drug before attending a health centre. However, recent studies in the Gambia, Sri Lanka, Thailand, and Zambia have demonstrated that chloroquine can safely be given by parenteral routes even to children with severe falciparum malaria (*22*, *24–26*, *28–30*).

Chloroquine should not be used if the infection has "broken through" chloroquine prophylaxis, if it does not appear to be responding to chloroquine treatment, or if there is any doubt about the origin of the infection. Clinicians may prefer to use quinine in all cases of severe falciparum malaria because of the rapid spread of chloroquine resistance and the risk of newly emergent resistance, even when the infection has been acquired in a predominantly chloroquine-sensitive area of the world.

(Recommendation 9.4.2.)

4.4.4 *Sulfadoxine/pyrimethamine*

This is available for intramuscular injection as a formulation containing 200 mg sulfadoxine plus 10 mg pyrimethamine in a 2-ml ampoule. It has undergone preliminary trials in adults and children in Benin, Brazil, Mali, Mozambique, and Thailand and has been found to clear parasitaemia as quickly as chloroquine (*31*, *32*). The combination acts only on the late trophozoite and schizont stages, which raises theoretical concern that parasites might already be sequestered in deep vascular beds and causing severe organ or tissue dysfunction before they are killed by the drug combination. This would be undesirable in patients with severe disease. The intramuscular preparation is very viscous and its administration is painful. Unlike chloroquine, it has no antipyretic effect so that patients also require antipyretic treatment.

Intramuscular preparations of sulfadoxine/pyrimethamine have proved effective in preliminary clinical trials. This combination may have been overlooked because of unjustified assertions that it was slow-acting. Further clinical studies are needed in areas where *P. falciparum* is sensitive to this combination. Despite some theoretical disadvantages, such an intramuscular formulation could be valuable in the treatment of chloroquine-resistant falciparum malaria and for patients who cannot swallow tablets.

(Recommendation 9.4.3.)

4.4.5 *Artemisinin and its derivatives*

Formulations of artemisinin derivatives, such as intravenous artesunate and intramuscular artemether, as well as suppositories of artemisinin have all shown rapid antimalarial action *in vivo* and have proved effective in the treatment of severe falciparum malaria in China (*33*). Unfortunately, these promising compounds have not yet been evaluated adequately outside China and are not generally available.

4.4.6 *Quinidine*

In vitro MICs of quinidine are lower than those of quinine against some strains of chloroquine-resistant *P. falciparum*, raising the possibility that quinidine might remain therapeutically effective even after the development of resistance to quinine. Parenteral formulations of quinine are not widely available in some areas (e.g., North America, Japan, and parts of Europe) but intravenous formulations of quinidine gluconate may be stocked by hospital pharmacies there, primarily for the treatment of cardiac tachyarrhythmias. In these situations, emergency treatment of severe falciparum malaria could be initiated with intravenous quinidine (*13*, *34*). In a preliminary study of intravenous quinidine in adults with severe falciparum malaria in Thailand, the drug was given in a loading dose of 15 mg/kg infused intravenously over 4 hours, followed by 7.5 mg base/kg infused over 4 hours every 8 hours. Complications included hypotension and hypoglycaemia. The former was reversed by slowing or stopping the infusion and by giving intravenous fluid (*13*). In this study, the volume of distribution and systemic clearance of quinidine appeared to be greater than those of quinine, with the result that plasma concentrations of quinidine were lower. As quinidine has a more marked effect on the myocardium than quinine, patients receiving quinidine infusion should be closely controlled, preferably with continuous electrocardiogram monitoring and with frequent measurements of blood pressure.

Quinidine is more toxic and more expensive than quinine. Whether in oral or parenteral formulations, it is an alternative to quinine *only* when quinine is not immediately available.

(Recommendation 9.4.4.)

4.5 Treatment of complications

4.5.1 *Anaemia*

This is an inevitable result of erythrocyte parasitization and its severity is proportional to the intensity of parasitaemia. In some areas, many patients, particularly children, are already anaemic from other causes or from repeated previous attacks of malaria even before they develop severe malaria. This may be alleviated by exchange blood transfusion but the risks this entails have increased greatly in recent years with the increased prevalence of human immunodeficiency virus (HIV) in many populations. When assessing the need for transfusion, the clinical condition of the patient as well as the initial haematocrit and parasitaemia must be taken into account.

Where fresh, pathogen-free compatible blood is readily available, transfusion with packed cells or whole blood should be considered when the haematocrit falls towards 20% (erythrocyte volume fraction, 0.2). Exchange transfusion is a safe way of correcting the anaemia without precipitating pulmonary oedema in those who are fluid overloaded or have been chronically and severely anaemic. It is important to include the volume of transfused blood in the calculation of overall fluid input. Fast-acting diuretics such as furosemide can be given intravenously at a dose of 1–2 mg/kg of body weight to promote diuresis during the transfusion. Compatible donor erythrocytes may be very rapidly eliminated in some patients recovering from malaria; this phenomenon is not attributable to quinine-mediated haemolysis and is not an indication for stopping quinine treatment (*35*).

Criteria for transfusion should be much more stringent in areas with a high prevalence of HIV and inadequate screening facilities for blood products.[1] Studies of patients who will not allow themselves to be transfused during surgery suggest that, after loss of more than two-thirds of the blood volume, the use of plasma expanders and oxygen alone cannot compensate for the cardiovascular effects and loss of oxygen transport. In these circumstances the risk of death is high. A haematocrit of 15% (erythrocyte volume fraction, 0.15)

[1] Relatives and friends are often the only source of donated blood in rural areas of the tropics. Older people, who are less or no longer sexually active, may pose a lower risk of HIV transmission by blood transfusion.

in a normally hydrated adult or child appears to be an absolute indication for blood transfusion, but transfusion may also be required at higher values if the patient's condition is deteriorating and there is evidence of shock and hypoxia. In many communities, however, chronic anaemia is common and results in a greater tolerance by individuals of low haematocrit levels.

If attempts to improve oxygenation and correct hypoxaemia with colloid infusions have failed, the assessment of the clinical condition (shock, cardiac failure, hypoxia) rather than an arbitrary haematocrit value should be used as the indication for transfusion. ***(Recommendation 9.4.5.)***

4.5.2 *Disseminated intravascular coagulation (DIC)*

This condition is commonly reported among imported cases of severe falciparum malaria in nonimmune subjects, but is relatively rare in tropical endemic areas. For example, evidence of disseminated intravascular coagulation was found in less than 10% of patients with cerebral malaria in Thailand; the use of heparin proved dangerous in this situation. The best treatment is to transfuse fresh whole blood or concentrates of clotting factors and platelets. Exchange transfusion can be used in fluid-overloaded patients. The slow intravenous injection of 10 mg vitamin K is indicated if the prothrombin or partial thromboplastin times are prolonged. Drugs, such as aspirin and corticosteroids, which increase the risk of gastrointestinal bleeding, should be avoided in patients with severe malaria.

4.5.3 *Hypoglycaemia*

Hypoglycaemia complicates malaria in three clinical settings: in patients given quinine or quinidine, in pregnant women, and in patients (especially young children) with severe disease. There are increasing numbers of reports of hypoglycaemia from all countries. As hypoglycaemia may be asymptomatic or its manifestations confused with other symptoms and signs of severe malaria, blood glucose must frequently be checked, especially in the high-risk groups (*15*). If there is any doubt, the patient should be given a

therapeutic trial of intravenous 50% dextrose. A continuous infusion of 5% dextrose given as 80 ml/kg over 24 hours may prevent quinine-induced hypoglycaemia in children (*11*), but hypoglycaemia developed or recurred in adults in Thailand despite continuous intravenous infusions of 5% or even 10% dextrose (*36*). Glucagon is effective in reducing hypoglycaemia in a small number of cases. Intravenous administration of 50% glucose is always effective, at least temporarily, in raising the blood glucose to normal, but its repeated use to treat recurrent hypoglycaemia may eventually lead to circulatory overload, hyperinsulinaemia, hypokalaemia, and acidosis. A clinical improvement after glucose administration is more frequent in adults than in children. Glucose may be given by nasogastric tube to unconscious patients (excessive volumes, leading to acute gastric dilatation, must be avoided), or by peritoneal dialysis in those undergoing this treatment for renal failure. Diazoxide, which inhibits insulin release, was ineffective but a somatostatin analogue, SMS 201-995, effectively blocked quinine-induced hyperinsulinaemia when given as a continuous intravenous infusion (*37*) or, more conveniently, by a single subcutaneous injection (R.E. Phillips, personal communication). This therapeutic approach is particularly attractive for the treatment of patients who are severely hypoglycaemic but fluid overloaded and in whom repeated injections of hypertonic glucose solution might precipitate pulmonary oedema.

4.5.4 *Cerebral malaria*

Patients suffering from cerebral malaria require the highest possible level of nursing care available as they are unconscious and liable to convulsions, vomiting, aspiration pneumonia, and other complications of prolonged immobility. They should be nursed on their sides, with the airway protected, and should be turned at least every two hours. The level of consciousness graded according to the Glasgow Coma Scale (*38*), pulse, blood pressure, temperature, central venous pressure, urine output, fits, and other clinical signs should be recorded frequently. Recent studies have shown that cerebral oedema does not play a significant role in the pathophysiology of cerebral malaria (*39*); it appears to be very uncommon except as a terminal phenomenon or in severely ill patients who have been ventilated and dialysed (*40*).

A number of potentially harmful remedies, based on outmoded hypotheses of unproven validity, have been recommended for the treatment of cerebral malaria. The use of corticosteroids, especially dexamethasone, had been fashionable since the 1960s in the belief that their anti-inflammatory effect would reduce cerebral oedema. This hypothesis has been tested in two double-blind studies in patients with cerebral malaria, using a moderate dose of approximately 2 mg/kg and a high dose of approximately 11 mg/kg of dexamethasone, given by intravenous injection over 48 hours (*1*, *41*). A reduction in death rates was not observed in either study. Both studies have been criticized on various grounds (*42–44*), but the serious side-effects of dexamethasone, such as prolonged unconsciousness, gastrointestinal bleeding, and increased incidence of secondary bacterial infections, were not balanced by a reduction in mortality. The use of this drug is therefore no longer justified.

Similar side-effects have been observed during studies of high-dose corticosteroids used in septicaemic shock and intracerebral haemorrhage (*45–47*). Corticosteroids have also been suggested for the treatment of haemolysis, blackwater fever, algid malaria, thrombocytopenia, and pulmonary oedema, but no benefit has been proved. Other osmotic or diuretic agents, such as mannitol and urea with invert sugar, aimed at reducing cerebral oedema, have not been proved to be beneficial and carry the risk of producing electrolyte disturbances and circulatory overload (*48*). Low-molecular-weight dextrans can reduce blood viscosity but this effect is unnecessary in patients with severe malaria, whose blood viscosity is already reduced because of the inevitable anaemia. Dextrans are contra-indicated in patients with thrombocytopenia and bleeding diatheses. More information is needed about the effects of epoprostenol and its synthetic analogues, which have been used in a few patients with severe malaria (*49*).

4.5.5 *Disturbances of fluid, electrolyte, and acid–base balance*

Even in temperate climates, patients with severe falciparum malaria may become dehydrated through failure to drink, increased imperceptible losses of fluids during high fever and, in some cases, profuse vomiting and diarrhoea. The resulting hypovolaemia will be manifested as postural hypotension, low jugular venous pressure, reduced ocular tension and tissue turgor, and reduced urine volume with high specific gravity. Associated abnormalities include

hyponatraemia and hypoalbuminaemia. Relative or functional hypovolaemia may exist despite increased blood or plasma volume and normal total body water and extracellular fluid volume (*50–52*). Failure to rehydrate such patients may result in hypotension, shock, inadequate tissue perfusion, lactic acidosis, and renal failure. However, excessive fluid replacement together with hypoalbuminaemia and possibly neutrophil-mediated pulmonary capillary damage may cause pulmonary oedema. The danger of precipitating fatal pulmonary oedema can be overcome by cautious rehydration, taking into account the volume of transfused blood and the volume of fluid used as a vehicle for intravenous infusion of antimalarial and other drugs. Only isotonic fluid should be used. Urine output and specific gravity must be recorded and fluid balance checked against the patient's weight daily. If the jugular venous pressure is difficult to obtain, a central venous catheter should be introduced. Impending pulmonary oedema is indicated by respiratory distress, tachypnoea, and basal crepitations with or without a rise in central venous or pulmonary artery wedge pressure. The differential diagnosis for such oedema includes aspiration pneumonia and metabolic acidosis, which may be distinguished by chest radiography.

There are two types of pulmonary oedema, the treatments for which are different. Patients with normal or low pulmonary wedge pressures resemble those with adult respiratory distress syndrome and should be treated by mechanical ventilation with positive end-expiratory pressure. Patients with high pulmonary wedge pressures should be given potent intravenous diuretics, venesection or "physiological venesection" by inflation of cuffs on the limbs in rotation, or treatment with vasodilators such as isosorbide dinitrate or sodium nitroprusside.

About a third of the adult patients with cerebral malaria in a recent study in Thailand showed elevations in blood urea and serum creatinine concentrations (*28*). The majority of these patients were clinically hypovolaemic. Urine output was restored by cautious infusion of isotonic saline, without allowing the central venous pressure to rise by more than 50 mmHg. Patients refractory to this treatment were given increasing doses of slowly infused intravenous furosemide (up to a total dose of 1 g) and finally an infusion of dopamine (2.5–5.0 μg/kg per minute) into a central vein (*53*). If these measures failed to achieve a sustained increase in urine output, strict fluid balance was enforced and the patients were treated with

peritoneal dialysis (*28, 54*). Indications for dialysis included hyperkalaemia, fluid overload, metabolic acidosis, and clinical manifestations of uraemia. Haemodialysis and haemofiltration have been used successfully and have theoretical advantages over peritoneal dialysis in severe malaria. The initial doses of antimalarial drugs should not be reduced in patients with renal failure, but maintenance doses may need to be reduced after 24 hours of treatment. If blackwater fever develops, the kidney may be damaged by passage of the products of massive intravascular haemolysis. Some nephrologists favour the use of mannitol and bicarbonate as in the treatment of myoglobinuria (*48*).

Lactic acidosis in severe malaria may result from impaired tissue perfusion caused by microvascular obstruction by parasitized erythrocytes, hypovolaemia, reduced hepatic clearance of lactate, and lactate production by parasites. Treatment should be aimed at improving perfusion and oxygenation by correcting hypovolaemia, clearing the airway, increasing inspired oxygen concentrations, and treating septicaemia, a frequently associated complication. Dichloroacetate, which stimulates pyruvate dehydrogenase principally in skeletal muscle, has been suggested for the treatment of lactic acidosis (*55*). Severe acidosis indicated by arterial pH less than 7.2 can be treated by cautious infusion of sodium bicarbonate or trometamol.

Hypotension and shock may develop in severe malaria as a result of pulmonary oedema, massive gastrointestinal haemorrhage, splenic rupture, or uncorrected gross dehydration. Some patients are hypotensive with cold, clammy, cyanosed extremities, conforming to the classical description of "algid malaria". These patients are also likely to be suffering from Gram-negative septicaemias, to which patients with severe falciparum malaria seem particularly prone (*1*). Haemodynamic problems should be corrected by giving plasma expanders, inotropic agents, and selective vasoconstrictors such as dopamine. Appropriate antimicrobial combinations include benzylpenicillin with cloxacillin, and gentamicin or cefuroxime.

4.5.6 *Exchange transfusion in hyperparasitaemia*

The mortality in presumed nonimmune patients with falciparum malaria is more than 60% when asexual parasitaemias rise above 500 000/ml (approximately 10% of erythrocytes parasitized) (*56*). Full or partial exchange transfusion has been proposed to treat such

patients. More than 30 patients have been treated since 1974 by transfusion using manual methods, haemodialysers and cell separators. The technique requires large volumes of blood but seems able to reduce parasite load rapidly, often with signs of clinical improvement such as recovery of consciousness and increased urine production. Exchange transfusion can correct anaemia without precipitating circulatory overload, can restore clotting factors and platelets, and may remove toxic metabolites and circulating mediators and toxins. There is growing experience and confidence in this technique but the practical difficulties of employing exchange transfusion in tropical endemic areas are formidable. The necessary volume of fresh, compatible, pathogen-free blood may be impossible to obtain, and there are inherent dangers in exsanguination and transfusion where there is inadequate clinical supervision. The level of hyperparasitaemia at which exchange transfusion is indicated varies widely in different epidemiological situations.

Full or partial exchange transfusion for hyperparasitaemia is not recommended unless pathogen-free blood is available, the patient is severely ill as well as being hyperparasitaemic, and the clinical facilities are adequate.

(Recommendation 9.4.6.)

4.5.7 *Severe falciparum malaria in pregnancy*

Falciparum malaria in the third trimester in nonimmune women has a poor prognosis. Uterine and fetal monitoring may reveal asymptomatic uterine contractions, fetal tachycardia, and late deceleration of fetal heart rate in relation to uterine contractions, indicating fetal distress (*15*). Hypoglycaemia is common and may be asymptomatic. Correction of maternal hypoglycaemia may cure fetal bradycardia and lowering maternal fever may relieve signs of fetal distress. As placental function may be impaired and intense parasitization of the placenta may threaten the life of the mother and fetus, obstetrical advice should be obtained about possible induction of labour, the speeding up of the second stage of labour with forceps or a vacuum extractor, and even Caesarean section (*57*). Acute pulmonary oedema may occur before delivery or immediately after delivery with the sudden increase in peripheral vascular resistance that accompanies separation of the placenta. Fluid replacement must be strictly controlled to avoid circulatory overload in women going into labour.

4.6 Management of severe and complicated malaria at various levels of health care

If patients with severe and complicated malaria are to receive the best possible treatment, there must be appropriate health care and an effective referral system from the community to the central hospitals. Responsibilities within this system will differ, since the availability of trained and competent personnel as well as the facilities for diagnosis and for the use of parenteral medication vary considerably at different levels of the health services. The following indicates how staff at each level of the services can approach the diagnosis and management of severe malaria according to their training and clinical competence.

4.6.1 *Facilities intended to provide minimum care*

Such facilities are most frequently found at the peripheral or community level. Commonly there is a paid health post attendant or a community health worker, who may be a volunteer. Usually, such persons have had limited training and are not expected to be able to elicit or interpret a detailed medical history, carry out more than a superficial examination, or apply sophisticated clinical judgement. By definition there are no laboratory facilities, and only oral medications, or possibly suppositories, are available. Guidelines for treatment are given in Table 3.

The principal responsibility at such facilities is prompt diagnosis and adequate treatment for persons with fever. The personnel involved should be able to recognize, or at least strongly suspect, severe and complicated malaria; should be able to bring down the body temperature, especially in children, by tepid sponging and the use of antipyretics; and should be able to give a first dose of a blood schizontocidal drug by mouth. They should be able to recognize patients who require referral and give appropriate guidance and assistance. Referral may be either to a dispensary or health centre or to an adequately equipped hospital according to the severity of disease.

The criteria for referral to an intermediate-care facility include: (*a*) persistent vomiting and inability to retain oral medication; (*b*) inability to eat or drink; and (*c*) failure to respond to initial treatment.

The criteria for referral to maximum-care facilities include: (*a*) difficulty in talking, sitting up, standing, or walking without any

Table 3. Chemotherapy of severe falciparum malaria in adults and children at the peripheral or community level

CHLOROQUINE-SENSITIVE MALARIA	*CHLOROQUINE-RESISTANT MALARIA OR ORIGIN UNKNOWN*
Chloroquine Tablets or syrup by mouth—10 mg base/kg body weight (or, if patient cannot reliably take oral medication, crushed tablets or syrup by nasogastric tube,[a] same dosage), then refer patient to higher level for parenteral treatment, *or* continue with 5 mg/kg 6, 24, and 48 hours later.	**Quinine** Tablets by mouth—10 mg salt/kg body weight (or, if patient cannot reliably take oral medication, crushed tablets by nasogastric tube,[a] same dosage), then refer patient to higher level for parenteral treatment, *or* continue 10 mg salt/kg, 8-hourly, to complete 7 days' treatment.
OR	**OR**
Quinine, mefloquine, or sulfadoxine/pyrimethamine As in right-hand column.	**Mefloquine** Tablets by mouth—15 mg base/kg body weight (maximum 1000 mg) (or, if patient cannot reliably take oral medication, crushed tablets by nasogastric tube,[a] same dosage).
	OR
	Sulfadoxine/pyrimethamine (*not* for pregnant or lactating women) Tablets by mouth—sulfadoxine 25 mg/kg body weight + pyrimethamine 1.25 mg/kg (or, if patient cannot reliably take oral medication, crushed tablets by nasogastric tube,[a] same dosage).

[a] If skilled supervision is available (the position of the nasogastric tube must be carefully checked).

other obvious cause; (*b*) unexplained heavy bleeding; (*c*) passage of small quantities of or no urine, or passage of dark urine; (*d*) a change of behaviour, confusion, or drowsiness; (*e*) altered consciousness or coma; (*f*) convulsion(s); (*g*) jaundice and/or severe anaemia; (*h*) circulatory collapse or shock; and (*i*) difficulty in breathing.

A safe suppository formulation of an antimalarial drug would be most valuable for use at the periphery of the health services.

(Recommendation 9.4.7.)

4.6.2 *Facilities intended to provide intermediate care*

Such facilities are generally dispensaries and health centres such as exist in a wide range of geographical and epidemiological settings, including isolated areas at the periphery, which may make them difficult to reach, especially during the heavy rains and floods that

coincide with the peak malaria transmission period. Guidelines for treatment of severe malaria at this level are given in Table 4.

Table 4. Chemotherapy of severe falciparum malaria in adults and children at the intermediate level of the health service

CHLOROQUINE-SENSITIVE MALARIA	*CHLOROQUINE-RESISTANT MALARIA OR ORIGIN UNKNOWN*
Chloroquine Injection—3.5 mg base/kg body weight, 6-hourly, intramuscularly or subcutaneously; change to oral route as soon as patient can swallow tablets, to complete total dose of 25 mg base per kg over 30 hours. **OR** **Quinine** As in right-hand column.	**Quinine**[a] Injection—20 mg dihydrochloride/kg body weight (loading dose)[b] intramuscularly (divided sites, anterior thigh), then 10 mg dihydrochloride/kg, 8-hourly[c] until patient can swallow tablets, then quinine tablets—approx. 10 mg salt/kg, 8-hourly, to complete 7 days' treatment.

[a] In areas with quinine-resistant *P. falciparum* (e.g., Thailand) add oral tetracycline 250 mg, 6-hourly, for 7 days as soon as the patient can swallow tablets; but *not* for pregnant women or children under 8 years old.
[b] Loading dose should not be used if the patient has received quinine or mefloquine within the previous 24 hours.
[c] If the patient still needs parenteral therapy after 48 hours, halve the maintenance dose to 5 mg/kg.

Facilities for parasitological diagnosis and other laboratory support may be available. Personnel may be expected to perform simple examinations and to exercise rather more clinical judgement than at the lower level. Parenteral treatment by intramuscular or subcutaneous injection may be available but not intravenous therapy. The staff at this level would therefore not be able to manage extremely severe cases, which must be referred to an adequately equipped hospital. Patients are referred to this level from facilities providing minimum care according to the criteria given above; in addition, some patients will present directly because of severe illness or because of failure to respond to previous treatment.

There are three major principles for the management of severe and complicated malaria at this level: (*a*) recognition or confirmation of severe malaria; (*b*) intramuscular or subcutaneous injection of antimalarials; and (*c*) rapid referral when necessary.

Patients with coma, jaundice, and anaemia may be referred after the diagnosis of *P. falciparum* malaria has been confirmed by laboratory examination and after intramuscular or subcutaneous therapy has been given. Referral of severely ill patients, however, should not be delayed by diagnostic procedures after the initial malaria treatment. The choice of antimalarial drug will depend on

national policy, based on the drug-sensitivity pattern of parasites in the area.

Correct medical management of convulsions and hyperpyrexia and appropriate nursing care are possible at the intermediate level.

4.6.3 *Facilities intended to provide the maximum possible care*

Such facilities may be district, provincial or central hospitals. Patients are referred from the two previously described types of facilities and from the private medical sector; they may also present directly to the outpatient clinics.

In these facilities, adequate management of severe and complicated malaria should be possible. Staff should be competent to take a detailed history, make a comprehensive physical examination, and carry out various investigations. Basic parasitological, biochemical, haematological, bacteriological, and radiographic services should be available.

A wide range of antimalarial drugs should exist in these facilities, and intravenous therapy is possible (see Table 5).

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Table 5. Chemotherapy of severe falciparum malaria in adults and children at the highest level of the health service

CHLOROQUINE-SENSITIVE MALARIA	*CHLOROQUINE-RESISTANT MALARIA OR ORIGIN UNKNOWN*
Chloroquine Infusion—10 mg base/kg body weight in isotonic fluid by constant-rate intravenous drip over 8 hours, followed by 15 mg base/kg by same means over 24 hours. *or* Infusion—5 mg base/kg in isotonic fluid by constant-rate intravenous drip over 6 hours, repeated immediately every 6 hours to a total dosage of 25 mg base/kg over 30 hours. **OR** **Quinine** As in right-hand column.	**Quinine**[a] Infusion—7 mg dihydrochloride/kg body weight (loading dose)[b] intravenously by infusion pump, followed immediately by 10 mg dihydrochloride/kg diluted in 10 ml/kg isotonic fluid by constant-rate intravenous drip over 4 hours, repeated 8-hourly (maintenance dose)[c] until patient can swallow tablets, then quinine tablets—approx. 10 mg salt/kg, 8-hourly, to complete 7 days' treatment. *or* Infusion—20 mg dihydrochloride/kg body weight (loading dose)[b] in isotonic fluid by constant-rate intravenous drip over 4 hours, then 10 mg dihydrochloride/kg by same means over 4 hours, 8-hourly, until patient can swallow tablets, then quinine tablets—approx. 10 mg salt/kg, 8-hourly, to complete 7 days' treatment. *or* Infusion—10 mg gluconate/kg body weight (loading dose)[b] in isotonic fluid by constant-rate intravenous drip over 1–2 hours, followed by 0.02 mg gluconate/kg per minute intravenously by infusion pump for 72 hours or until patient can swallow tablets, then quinine tablets—approx. 10 mg salt/kg, 8-hourly, to complete 7 days' treatment. **OR** **Quinidine** Infusion—15 mg gluconate/kg body weight (loading dose)[b] by constant-rate intravenous drip over 4 hours, then 7.5 mg gluconate/kg by same means over 4 hours, 8-hourly, until patient can swallow tablets, then quinidine sulfate tablets, 7.5 mg base/kg, 8-hourly, to complete 7 days' treatment.

[a] In areas with quinine-resistant *P. falciparum* (e.g., Thailand) add oral tetracycline 250 mg, 6-hourly, for 7 days as soon as the patient can swallow tablets; but *not* for pregnant women or children under 8 years old.

[b] Loading dose should not be used if the patient has received quinine or mefloquine within the previous 24 hours.

[c] If the patient still needs parenteral therapy after 48 hours, halve the maintenance dose to 5 mg/kg.

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5. MALARIA CHEMOPROPHYLAXIS

Chemoprophylaxis as a malaria control strategy has become progressively more difficult in recent years, owing in part to the expansion of drug resistance and the increasing recognition of the adverse side-effects of several prophylactic drugs.

The range of drugs available for suppression includes the 4-aminoquinolines (chloroquine), the dihydropteroate-synthase inhibitors (sulfones and sulfonamides), the tetrahydrofolate-dehydrogenase inhibitors (pyrimethamine and proguanil), mefloquine, and doxycycline. There is, however, no drug that guarantees 100% protection in any endemic area (*1*).

Most of these drugs are schizontocides, which must reach and be maintained at a suitable concentration in the blood to be effective against the parasite when it enters the blood, i.e., 6–14 days after initial exposure to infection. Preferably, these concentrations should be maintained at a steady state. This is usually achieved with chloroquine by a weekly regimen of 5 mg of base per kg of body weight (300 mg for adults of normal weight, and in proportion to

body weight for children). A loading dose of 5 mg base per kg of body weight on the first two days has been recommended by certain groups to accelerate the establishment of steady-state drug profiles and to ensure that blood levels of the drug are always above the minimum effective concentration required to kill the blood parasites.

5.1 Problems associated with chemoprophylaxis

Two decisions are required before a recommendation can be made about chemoprophylaxis: (*a*) whether to resort to it, and (*b*) which is the most appropriate drug to use. Ideally, both decisions should be based on precise knowledge of the risk of malaria and of the protective efficacy and risk of toxicity of the different chemoprophylactic regimens. Information in all these areas is incomplete and experts do not agree in every case. Furthermore, not all drugs are available in every country. For these reasons, national advisory bodies differ in their specific recommendations.

5.1.1 *Drug resistance*

Resistance of *P. falciparum* to the tetrahydrofolate-dehydrogenase inhibitors—pyrimethamine and the biguanides, proguanil and chlorproguanil—was recognized in the 1950s in many areas of the world. Several hypotheses for the development of this resistance have been proposed. They include the use of the drugs for mass drug treatment, for prophylaxis, and for deployment as sporontocides (for review, see *2*). It has been debated whether resistance to pyrimethamine and the biguanides has spread geographically or simply arisen in many foci. It has also been suggested that pyrimethamine resistance would not be stable if the drug was withdrawn from use. This hypothesis is based on laboratory studies, which show that pyrimethamine-resistant parasites may be at a biological disadvantage compared with sensitive ones (*3*) and on the unique longitudinal field studies carried out in the north-east of the United Republic of Tanzania by Clyde (*4*). Observations from other studies carried out in that country and elsewhere, however, suggest that reversion to susceptibility does not occur.[1]

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[1] KOUSNETSOV, R.L. ET AL. *Spread of pyrimethamine-resistant strains of Plasmodium falciparum into new areas of North-East Tanzania with absence of drug pressure* (unpublished WHO document WHO/MAL/80.926).

Resistance to the biguanides appears to be more complex. Unlike pyrimethamine, these drugs have a marked effect on the primary tissue stages of at least *P. falciparum*, *P. vivax* and *P. ovale*. They may therefore have a causal prophylactic activity in contrast to the suppressive prophylactic activity shown by pyrimethamine. Studies both in the laboratory and in the field suggest that causal prophylactic activity may be retained against *P. falciparum* infections even when there is resistance in the blood-stage parasites (*2*). Cross-resistance between pyrimethamine and proguanil occurs in the blood stages of *P. falciparum*, but this is not absolute. Some strains resistant to chloroquine and proguanil, however, are sensitive to pyrimethamine (*2*). It has been suggested that chloroquine-resistant *P. falciparum*, in contrast to pyrimethamine-resistant *P. falciparum*, has a biological advantage over sensitive parasites. This hypothesis has been used to explain the spread of chloroquine resistance in the field (for review, see *2*), but the evidence for it is only circumstantial. It has also been suggested that chemoprophylaxis, mass drug administration, and "incomplete therapy" may lead to the development of resistance to chloroquine or hasten its intensification or geographical spread. Both Onori et al. (*5*) and Draper et al. (*6*) have suggested that intermittent chemosuppression with evidently subcurative doses in the chloroquinized salt programmes for mass drug administration in the United Republic of Tanzania resulted after several years in selection for a considerable degree of resistance.

5.1.2 *Compliance and the logistics of delivery*

Compliance has been difficult to achieve and even more difficult to sustain in virtually all documented experience with chemosuppression, whether in children or in adults. The factors that contribute to poor acceptability or compliance include bitter taste, as with chloroquine; side-effects, as with chloroquine-associated pruritus; objections to drug use, especially during pregnancy and lactation; and general disinclination to take medicine to prevent illness (*7*). Well supervised studies report that compliance rarely exceeds 90% and generally ranges from 30% to 60%.

A major challenge for malaria chemosuppression programmes is to develop the logistics to ensure a reliable supply of drugs. Most programmes have attempted total coverage of a given population group, such as children less than 5 years old or pregnant women. In

such instances, drugs must be available to the target population and either their administration must be supervised or effective health education given to promote and sustain their use.

If satisfactory compliance can be achieved, there is evidence that chemoprophylaxis may be effective in young children. Greenwood et al. (*8*) have reported that community-based chemoprophylaxis in the Gambia reduced malaria deaths more significantly than did community-based malaria treatment. The striking observation from this study was that children dying of malaria had a mean duration of illness of 3 days. A limitation of the study was that the fee charged for antimalarial treatment might have resulted in the mothers' delaying seeking care for their sick infants. If both prophylaxis and treatment had been free, the response of the public might have improved. As in previous studies, children who received chemoprophylaxis had a significantly higher erythrocyte volume fraction, or haematocrit, and lower rates of splenomegaly.

Prevention of death in children with malaria at present focuses in many parts of the world on the rapid recognition and prompt treatment of acute febrile illness, and depends on the reliability of the clinical diagnosis of malaria in fever patients when microscopy is not available. This assumes that malaria mortality is more closely related to fever than to parasitaemia, with its less characteristic symptomatology. In some specific situations, prophylaxis of children under 5 years of age may be appropriate, if problems of coverage, compliance and cost can be overcome; but in other areas, a better strategy might be to develop primary health care units at the periphery to make it possible to treat malaria promptly with effective medication.

5.1.3 *Impairment of the acquisition of immunity*

Early studies suggested that children who had taken drugs prophylactically had more severe malaria if they became infected and developed the disease (*9*), implying that their immunity might have waned rapidly without antigenic stimulation. However, subsequent studies have found that, while children who had received prophylaxis may have had low levels of immunoglobulins and specific antibodies, their infections were less severe clinically than those of children who had not received prophylaxis (*10–12*). Most studies suggest that, as chemosuppression is never complete,

sufficient exposure to parasites occurs to stimulate the immune system and to maintain some level of actively acquired immunity.

It has been shown that *P. falciparum* infections may induce a degree of immunosuppression (*13*). Some antimalarials, such as chloroquine, also have well recognized immunosuppressive effects (*14*). Thus both parasitaemia and drugs used for prophylaxis may impair immune responses. These factors merit further study, especially in children.

5.1.4 *Prophylactic efficacy of antimalarial drugs*

The efficacy of chemoprophylaxis may be determined and monitored through controlled trials or by analysing data on failures of prophylaxis in travellers (*1*). Yet, because controlled prophylaxis trials are time-consuming, labour-intensive, and expensive, they can be carried out only infrequently, in a few locations, and they usually include very small population groups. Studies in travellers can be difficult to interpret because of uncertainty regarding compliance with prescribed medication and degree of malaria exposure. The prophylactic efficacy of a given drug regimen has therefore often been inferred from the drug's therapeutic effect, although that does not, of course, apply to drugs used only for prophylaxis (e.g., proguanil).

The efficacy of a drug, the adverse reactions it causes, and its suitability for use in combinations are all influenced by its pharmacokinetics and metabolism. The design of prophylactic regimens should therefore be based on sound pharmacokinetic knowledge to maintain optimal efficacy and to reduce or prevent toxicity. Unfortunately, insufficient data are available on the metabolism of most antimalarial drugs. Surprisingly little is known about the wide individual variations observed in the kinetics of these drugs in children and the elderly and about their interactions with other drugs.

5.1.5 *Adverse reactions*

Serious adverse reactions to several important antimalarial drugs have been documented in the last few years. Agranulocytosis and hepatitis related to the use of amodiaquine and severe cutaneous

adverse reactions related to the use of sulfadoxine/pyrimethamine have led to both of these drugs no longer being recommended for chemoprophylaxis for the reasons discussed in sections 3.2.2 and 3.3.1.1, respectively. The case of mefloquine has been discussed in section 3.2.5.2.

Doxycycline, a structural isomer of tetracycline (see section 3.2.7), may cause ossification disorders and discoloration of developing teeth, and its use should therefore be avoided in pregnant women and children under the age of 8 years. It has also been reported to cause skin photosensitivity, leading to abnormal sunburn reactions (*15*).

Agranulocytosis, sometimes leading to death, has been reported following the prophylactic use of the combination of dapsone and pyrimethamine. This combination has been widely used for prophylaxis in southern Africa, Malaysia, and the United Kingdom, both alone and in an *ad hoc* combination with chloroquine. The frequency of such reactions appears to be greater following the use of 2 tablets per week than with the currently used dose of 1 tablet per week (each tablet containing 100 mg dapsone and 12.5 mg pyrimethamine). A survey in Sweden detected agranulocytosis in 1 in 2000 persons using 2 tablets per week for prophylaxis (*16*).

These observations have led to studies using low doses of dapsone to minimize or eliminate the side-effects. A 10-mg dose of dapsone, in combination with 200 mg proguanil daily, has recently been shown to give effective protection in Papua New Guinea to workers from a nonmalarious highland area transported to a lowland area with high malaria transmission (K.H. Rieckmann, personal communication). In this study, which was conducted for 12 weeks, neither agranulocytosis nor mouth ulcers, which may result from proguanil use, were observed. In fact, no adverse reactions of any type were reported although only 280 volunteers, a relatively small number, were studied.

5.2 Chemoprophylaxis for special groups

As a consequence of the above problems, chemoprophylaxis is only recommended at present for special risk groups, notably pregnant women, nonimmune travellers, and nonimmune persons living in closed communities in endemic areas for fixed predetermined periods (e.g., labour forces and police and army units).

5.2.1 *Pregnant women*

The risks of complication of *P. falciparum* infection are increased during pregnancy (*17–19*). Anaemia, abortion, stillbirths, prematurity, and low birth weight commonly occur, although it is not clear whether all these conditions relate to the malaria infection. In some circumstances, *P. falciparum* infection may be severe during pregnancy, presumably as a result of depressed maternal immunity. This risk of severe or fatal maternal disease is greatest in areas of unstable transmission. In contrast, pregnant women in areas of Africa with highly endemic malaria are generally not at greater risk of severe disease, but their susceptibility to malaria does increase during pregnancy, particularly among primigravidae who suffer from anaemia and the various complications of chronic parasitaemia.

Plasmodium infection has been suggested as a cause of abortion in malaria-endemic areas. However, the majority of such abortions occur in the first trimester, when surveillance is the most difficult; the true magnitude of the problem is unknown. There was no association between malaria infection and stillbirths among 6427 deliveries in the Gambia (*17*).

Placental infection with *P. falciparum* has been associated with low birth weight in various studies in Africa. This association is strongest in lower parities. Birth weight is one of the most important determinants of infant survival in most developing countries and consequently merits full attention in malaria control programmes. Low birth weight, however, can be caused by many factors. Malaria parasitaemia cannot be assumed to be the only or even the most important cause and it may be that only a proportion of cases are preventable by antimalarial measures.

Strategies for reducing the impact of infection and disease due to malaria during pregnancy have generally relied on chemoprophylaxis. There is evidence from Nigeria that the risk of maternal anaemia is reduced by chemoprophylaxis, particularly during the early stages of pregnancy (*20*). Higher haemoglobin levels and lower parasitaemia rates have also been observed in Kenya among pregnant women who said that they were taking prophylaxis, although compliance was low (*21*). Such an effect on maternal haemoglobin has also been observed with chloroquine prophylaxis in an area of Papua New Guinea where chloroquine-resistant *P. falciparum* was prevalent (B. Brabin, personal communication).

Prevention of low birth weight and reduction of the attendant risk of infant mortality by antimalarial chemoprophylaxis have not yet been demonstrated. Preliminary results from a study in Malawi suggest that women treated with mefloquine were most likely to clear placental malarial infections. Prophylaxis with mefloquine appeared also to be effective in controlling parasitaemia, including that of the placenta, but the impact of effective prophylaxis was variable, the nutritional state of the woman overshadowing placental infection as a risk factor for low birth weight.

Clearly a greater understanding of malaria in pregnancy is required to determine whether prophylaxis during pregnancy can be an effective strategy and where prompt treatment would be more effective and appropriate. Such information is essential for the targeting of these measures to the group most at need. For example, if fever due to malaria is detrimental to pregnancy, as may be the case in nonimmune women, prevention of infection and parasitaemia would be the priority and prompt treatment of any parasitaemia essential. If placental damage by malaria occurs early in pregnancy and if women seek prenatal care only in the second trimester, health care systems would have to develop more active programmes to reach the women most at risk. This should include intensive campaigns urging early prenatal care and emphasizing the risks to the fetus of severe malaria, anaemia, and malnutrition.

The acceptability and feasibility of chemoprophylaxis vary from one community to another and are major factors to be considered when developing appropriate strategies. Health care services generally discourage women from taking medicine during pregnancy. Also there is often confusion as to which medications are safe. Even with a relatively safe drug such as chloroquine, its acceptability in different cultures varies; in some communities, tradition dictates that bitter medicines such as chloroquine should be avoided during pregnancy. Drugs that cause side-effects in otherwise asymptomatic women are also likely to be avoided during pregnancy. Finally, in some communities, chloroquine is regarded as abortifacient and therefore to be avoided.

(See recommendation 9.5.1.)

5.2.2 *Nonimmune persons (e.g., travellers)*

In the past, it was often assumed that malaria chemoprophylaxis in nonimmune people was of benefit and without serious

complications and that, consequently, it was preferable to recommend prophylaxis to travellers whose risk of acquiring malaria was uncertain. In the current epidemiological situation, and given the lack of universally effective and safe chemoprophylactic drugs, a more careful weighing of the risk of acquiring a potentially fatal malaria infection against the toxicity and effectiveness of the available antimalarial drugs is now required. The many technical problems and the increasing number of nonimmune travellers at risk of malaria infection call for a systematic approach to the development of recommendations for their protection (*1*).

It is no longer true that prophylaxis is always better than no prophylaxis, nor is it true that a more effective but less safe drug is always preferable to a less effective but safer one. Also, certain drugs are contraindicated in certain groups or individuals so that it is recommended that pregnant women, very young children, and the very old should carefully consider the urgency and need to travel to areas where there is transmission of *P. falciparum*, and particularly of its drug-resistant strains. The elderly are also particularly at risk of adverse drug interactions, since many will be receiving antihypertensive and other cardioactive drugs, which are contraindicated with mefloquine prophylaxis. Chloroquine and proguanil at the recommended doses can, however, be given prophylactically to pregnant women and infants.

(See recommendation 9.5.2.)

If travel to malarious areas is unavoidable, travellers should be provided before their departure with the addresses of reliable medical services in the country of destination or should be covered by insurance for emergency repatriation. Persons who are known to be hypersensitive to an antimalarial drug or who are taking other drugs should consult a physician with specialized knowledge of the problem before their departure and consider whether their journey is essential. Persons who are immunodeficient or suffer from such diseases as lymphoma, leukaemia (even in remission) or Hodgkin's disease should ensure that adequate medical care is available at their destination and should seek such care immediately if they fall ill.

Since the parasites of malignant malaria (*P. falciparum*) incubate for 7–30 days, and those responsible for the more benign forms (mainly *P. vivax*) may incubate for even longer, a disease that starts less than 7 days after the first exposure is probably not malaria. As

the most important survival factor for persons who may have malignant malaria is early diagnosis and treatment, a nonimmune person who develops fever 7 days or more after the first possible exposure to malaria should seek prompt medical attention. The person concerned may have to remind the physician that the disease might be malaria because many doctors in nonmalarious countries have little experience of it.

In certain situations, the appropriate drugs and prompt medical attention may not be available and nonimmune persons may be advised to carry certain antimalarial drugs as "stand-by treatment". The stand-by treatment may be used as self-treatment or, preferably, after obtaining medical advice. As therapy may cause toxic reactions, travellers should resort to self-treatment only if they seriously suspect malaria and prompt medical attention is not available, and even then only as a temporary measure; they should still seek medical attention at the earliest opportunity and tell the physician what drug or drugs they have taken. The typical manifestations of malaria are bouts of high fever, lasting a few hours, starting dramatically with shaking chills, subsiding dramatically with profuse sweating, and reappearing at regular intervals, most commonly every 48 hours. However, the signs are often atypical during the first few days and are less typical in malignant than in benign malaria. Therefore the possibility of malaria should be considered in all otherwise unexplained fevers in nonimmune persons who have been exposed. After returning to a nonmalarious country, there is generally no justification for treating oneself; medical attention must be sought promptly.

The drugs recommended for prophylaxis, with the possible exceptions of proguanil and doxycycline, do not eliminate the liver stages of relapsing malaria infections, i.e., *P. vivax* in most of the malarious areas and *P. ovale* in West Africa. The liver stages can lead to relapses up to 3 years after exposure, but these relapses are not life-threatening and are susceptible to chloroquine. They can be prevented by primaquine; an antirelapse course of primaquine may be considered for persons who have been exposed to a relatively high risk for 6 months or more. Primaquine should be taken only under medical supervision. The adult regimen is 15 mg per day for 14 days.

The following summarizes the situation where chemoprophylaxis and "stand-by treatment" may be considered; detailed recommendations are given in *International travel and health:*

vaccination requirements and health advice, of which an updated edition is published by WHO every January (*22*).

(*a*) *Chemoprophylaxis and stand-by medicament not recommended.* Prophylactic and therapeutic drugs are not required for travellers to areas where transmission of malaria has not been reported or occurs only at a very low level, and where suitable diagnostic and therapeutic facilities are within easy reach.

(*b*) *Chemoprophylaxis not recommended but stand-by medicament to be available.* For short-term travellers to areas where transmission of malaria is low and diagnostic and therapeutic facilities are not readily available.

(*c*) *Chemoprophylaxis recommended but stand-by medicament not required.* For travellers to the following areas where chemoprophylaxis would be expected to be successful:

—areas with chloroquine-sensitive *P. falciparum*;
—areas with *P. vivax*, *P. malariae* or both, but not *P. falciparum*, where chloroquine will be the prophylactic agent and no alternative drug needs to be carried.

(*d*) *Both chemoprophylaxis and stand-by medicament recommended.* For travellers to areas where an appreciable risk of infection with *P. falciparum* exists, and where the drug used for prophylaxis may not be effective in preventing clinical illness in an appreciable number of cases. If adequate measures for personal protection can be ensured, it may be acceptable to rely on these methods without any chemoprophylaxis but with an appropriate stand-by drug.

(*e*) *Chemoprophylaxis may be considered with or without stand-by medicament.* It is difficult to make specific recommendations for travellers to the areas with serious risk of exposure to multidrug-resistant *P. falciparum*, particularly in view of the limited experience with drugs which may offer protection. In these situations different options are available. If adequate measures for personal protection can be ensured, it may be acceptable (as above) to rely on these methods without any chemoprophylaxis but with an appropriate stand-by drug. Alternatively, chemoprophylaxis with either mefloquine or doxycycline may be considered. In the event of illness, it is imperative for travellers to obtain treatment from a qualified medical practitioner.

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6. MONITORING SYSTEMS

Malaria control programmes require a coherent policy defining the use of malaria drugs. These policies need to incorporate locally relevant information on various issues to ensure that they are fully appropriate. These include:

—the procurement of drugs: drug availability, sources of supply, quality assurance;
—the deployment of drugs: logistic systems for transport and storage, which drugs are most appropriate for use at the various levels of the services;
—effective therapy and prophylaxis regimens for particular drugs, and definition of patient management in the health care system;
—monitoring systems for assessing drug use, compliance, adverse reactions, and efficacy.

The prerequisites for effective and sustainable monitoring systems are that they are efficient in the use of time and personnel and that they generate data useful to health care personnel and policy-makers.

The procurement and deployment of drugs are discussed in section 7 of this report. This section concentrates on the monitoring of drug efficacy and of adverse reactions to these drugs.

6.1 Monitoring drug efficacy

The efficacy of antimalarials is evaluated by *in vivo* observations of the susceptibility of human *Plasmodium* species to them. The standard *in vivo* tests of drug sensitivity (see *1*) may, however, not provide a perfect answer since:

(*a*) The tests measure the drug response of the infection rather than the response of the disease, since most *in vivo* testing has been conducted in mildly symptomatic patients. Some investigators, however, have included clinical assessment in the *in vivo* test for chloroquine sensitivity in areas of chloroquine resistance, producing particularly valuable information (*2*).

(*b*) They can only be performed in small samples because of eligibility criteria, e.g., no antimalarials must have been taken in the previous weeks, and the infection should be with a single species and of a minimum parasite density of 1000 asexual parasites per mm^3 of blood. Extensive follow-up is also required.

(*c*) Results can be confounded by patients' underlying immunity.

More operationally appropriate *in vivo* monitoring should incorporate the following:

—systematic early detection of treatment failures (including failure to respond clinically);
—investigation of treatment failures by simple but standardized methods (including past medical history and re-examination), and identification of cases of suspected drug resistance;
—clinical and parasitological evaluation of the effectiveness of the alternative treatment when a second-line drug is used in suspected treatment failures;
—simplified *in vivo* testing based on the minimum number of post-treatment checks and incorporating simple clinical assessment.

(See recommendation 9.6.4.)

In vitro tests of parasite susceptibility to antimalarial drugs provide a specific insight into parasite biology and the relationships between drug susceptibility and the pharmacokinetic properties of drugs. Experience in malaria control programmes has demonstrated, however, that *in vitro* testing cannot substitute for *in vivo* observations of malaria therapy and is inappropriate for making policy decisions on drug use. The optimal deployment of *in vitro* tests should be to define specific issues related to temporal and

geographical trends in the parasite's response to drugs. Such issues include:

—longitudinal follow-up of drug susceptibility of the parasite in areas where changes in drug policy are introduced compared with those where such changes are not implemented;
—monitoring the patterns of cross-resistance of the parasite to different drugs;
—the establishment of baseline data on the response of local parasite isolates to a new antimalarial drug.

(See recommendation 9.6.5.)

6.2 Monitoring adverse reactions

6.2.1 *General considerations*

A clinical and field evaluation of new drugs, using standardized protocols, is carried out in most countries before drugs are licensed and marketed. The first three phases of evaluation include an examination of the tolerance of the new drug in healthy volunteers and in patients, and its efficacy and safety first in mildly symptomatic and then in more severely ill patients. These studies can detect only the more common reactions to a drug since small numbers of patients are included. The long-term efficacy and safety of the drug must often be determined by postmarketing surveillance. Serious adverse reactions are mostly rare disorders, for which a measurement of risk needs time and the exposure of large numbers of people to the drug. For example, at least 15 000 people would have to be exposed to a drug to detect with a confidence level of 95% an adverse reaction that occurs at a rate of 1 in 5000 (*3*). In practice, this number is even greater because initial reports of such reactions to national authorities do not immediately alert specialists. Smaller case-control studies are an alternative to such cohort studies but confounding risk factors (e.g., administration of other drugs, underlying medical problems) are problematic. Adverse reactions are usually recognized following case reports published in the medical literature, frequently with a delay of 1–2 years between diagnosis and publication. It is often difficult to interpret the significance of such reports because the clinical criteria applied to different cases may not be comparable. Their main usefulness is as an alert to the possibility of an association with drug use. In

addition, cases of adverse reactions may not be recognized as such or may never be reported.

Comprehensive national drug registration provides a unique opportunity to monitor adverse reactions. The weaknesses of the system are under-reporting, inadequate information on individual cases, and misclassification of causality (*4*). Other approaches, such as the monitoring of prescriptions, case-control studies or studies of cohorts exposed to the drug, can be less satisfactory or even more time-consuming (*5*). The most valid and economical method may be follow-up studies of the users of drugs because the information is obtained directly from the patients and the reactions can be verified by review with the physicians and the hospital records (*6*). Users of antimalarial drugs for prophylaxis can readily be identified by contacting physicians who provide health advice to travellers or by surveys of travellers.

The major problems of postmarketing monitoring systems for detecting drug risks are:

—lack of awareness of the significance of first reports of adverse reactions;
—inadequate national registers, or failure to use them;
—difficulty of drawing epidemiologically valid conclusions; and
—inadequate recording or analysis of data.

Nevertheless, systematic postmarketing surveillance is essential to determine the safety of antimalarial drugs. The risk of adverse reactions is an important consideration when defining therapeutic and prophylactic guidelines, and resources must be committed to developing adequate surveillance systems. Such surveillance requires cooperation between the pharmaceutical industry, providers of health advice, and health practitioners in endemic and nonendemic countries.

(See recommendation 9.6.2.)

6.2.2 *Monitoring adverse reactions in endemic countries*

Much of the foregoing is applicable mainly to industrialized countries, from which a large number of travellers visit malaria-endemic zones. There is, however, an even greater need for the collection of information in the endemic countries, where the drugs are utilized on a large scale for the treatment of malaria. In such situations, procedures for the identification and follow-up of

suspected reactions are obviously less well coordinated and systematized than in the industrialized countries. There is, for instance, no uniformity in the information systems for documenting and monitoring drug consumption and its consequences in most endemic areas; each country has its own system and few have developed satisfactory reporting and recording services. There is a need to establish simple systems, particularly when a new drug is introduced into an endemic country for treatment.

(See recommendation 9.6.1.)

Recent experience in Thailand offers some pointers. The malaria control programme in that country established a monitoring system when the combination of mefloquine/sulfadoxine/pyrimethamine was introduced operationally in 1985 for the first-line treatment of falciparum malaria. Twelve cutaneous reactions, possibly related to the use of this combination, were reported between February 1985 and March 1986, following the administration of approximately 79 000 doses of the drug (see section 3.2.5.3). Four of the cases were severe, and two of these were diagnosed as Stevens-Johnson syndrome: one was a reaction to a small dose of sulfadoxine/pyrimethamine, aggravated by subsequent treatment with mefloquine/sulfadoxine/pyrimethamine, while the other was apparently caused by a single dose of the triple combination. It was recognized that the first patient, having exhibited a mild rash suggestive of sulfonamide sensitivity, should, under ideal circumstances, never have received the triple combination. However, it is clear that in most malaria-endemic countries, a variety of medications is commonly available and patients in peripheral areas are often treated by personnel who are not medically qualified.

(See recommendation 9.6.3.)

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7. PROCUREMENT AND DISTRIBUTION OF ANTIMALARIAL DRUGS

Most countries have some legal provisions for regulating the import, distribution, and use of pharmaceuticals. Often this legislation has been used to ration the outflow of scarce foreign exchange which in turn regulates the inflow of drugs, but now there is a growing awareness of the need to procure and distribute the most appropriate drugs and prevent the import of harmful ones. This is accomplished through the registration of products authorized for use in the country, medical need being a major criterion for registration in a number of countries. Both registration and legislation must be accompanied by the ability to evaluate the drugs submitted for registration. Many endemic countries lack the resources for this work and rely on the registration decisions made in the country where the drug is manufactured or already used (*1*). For example, the decision by the French authorities to register halofantrine was followed closely by approval in Congo, Côte d'Ivoire, and Togo.

Ministries of health have to decide which antimalarials are appropriate and when and how they should be used (*2*). The decision as to the level or levels of the health services at which a drug should be used is not a trivial one, since it determines the place to which a patient needs to go to receive a specific treatment as well as the quantity of drug needed. The cost and availability of the drug as well as the skills of the health staff required to administer the drug must also be considered. In the case of antimalarials, an additional consideration has to be the degree of resistance of local parasites to currently available antimalarials. Frequently, however, the data on which these decisions should be based are either not available or of poor quality so that decisions may be made on the basis of cost alone. In contrast, patient demand rather than medical need is the major factor in the selection of drugs in the private sector.

7.1 Prescription of antimalarials

Prescription of antimalarials is affected by three main factors: the prescriber's skill and experience, the availability of different antimalarials, and the patient's own demands and expectations. In some developing countries, only about 10–15% of outpatients are seen by a medically qualified person, drugs being taken by self-medication or prescribed by health staff whose level of education may be inadequate. Furthermore, the peripheral health facilities may be incapable of performing even the most simple laboratory tests needed to guide proper treatment. Self-medication (i.e., where a qualified prescriber is not consulted) may account for as much as half of the use of antimalarials, and this practice may be increasing. There is an urgent need, therefore, to provide prescribing information for health personnel, drug dispensers, and the public. This information must be up to date in view of the increasing frequency and spread of drug resistance in *P. falciparum*.

(See recommendation 9.7.1.)

7.2 Networks for distribution

In most countries there are typically four main networks through which antimalarial drugs are distributed:

(*a*) *The public sector*. This includes the ministry of health facilities, national malaria control programmes, national teaching hospitals, as well as specialized organizations such as the military and the police. Social security organizations that provide health care with government support also form part of the public sector even though they serve only their members. Typically, these facilities are funded from government revenues but patients are often asked to pay a user's fee at the time of consultation.

(*b*) *The private non-profit-making sector*. This is usually made up primarily of mission hospitals and other nongovernmental services. This sector often receives some financial support from the government but obtains the majority of its funding externally from nongovernmental organizations as well as from user charges.

(*c*) *The private commercial sector*. This is composed of private physicians, hospitals and clinics, private drug importers and pharmacies, and other outlets, such as general stores and drug depots, which are licensed to sell a limited range of drugs. Local manufacturers and subsidiaries of multinational companies also form part of this sector. It is usually self-financing, although there

may be significant subsidies from the government in the form of direct payments, tax concessions, preferential access to foreign exchange at special rates, or tariff protection from imports.

(*d*) *The private unofficial or informal sector*. This is composed of unofficial market and street sellers, distributors of pilfered drugs, occasionally distributors of counterfeit or adulterated drugs. Despite the illegality of such practices in most countries, these activities are usually tolerated and those who carry them out may be well integrated into the local community. Such distribution accounts for a significant portion of the antimalarial drugs consumed in many countries. Unofficial outlets of various types may account for as much as 25% of the drugs distributed; in some countries the percentage may be significantly higher and in rural areas may account for most of the drugs distributed.

The relative importance of each of these sectors varies between countries but globally it is possible to get a rough estimate of the relative importance of malaria control programmes as distribution mechanisms for chloroquine. The United Nations Industrial Development Organization (UNIDO) estimated in 1985 that approximately 1300 tonnes of chloroquine are produced annually.[1] On the basis of data from surveys submitted by governments, WHO estimates that approximately 300–400 tonnes are distributed annually through malaria control programmes,[2] i.e., approximately 25–30% of annual production.

While the use of antimalarials within the context of malaria control programmes is well documented, especially in Nepal[3] and Thailand,[4] little is known about the very significant part of antimalarial drug distribution through unofficial channels and the

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[1] *Technical and economic analysis of the manufacture of chloroquine phosphate* (unpublished document UNIDO/IS/518 of the Sectoral Studies Branch, Division for Industrial Studies, UNIDO, Vienna, 1985).

[2] KOUZNETSOV, R.L. *Trends in antimalarial drug consumption and requirements for antimalaria programmes in developing countries (1978–1989)* (unpublished WHO document WHO/MAL/88.1048).

[3] MILLS, A.J. *Economic study of malaria in Nepal: the cost-effectiveness of malaria control strategies* (unpublished report available from the Evaluation and Planning Centre, London School of Hygiene and Tropical Medicine, 1987).

[4] KAEWSONTHI, S. ET AL. *Costs and performance of malaria surveillance and monitoring in Thailand: a retrospective study based on apportionment of expenditure under budget headings* (unpublished document TDR/SER/PRS/5 of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 1988).

private sector. In some countries, such as Malaysia, where drugs are tightly controlled and prices of antimalarials other than chloroquine are high, the volume of antimalarials distributed through private channels is minimal. In contrast, in other countries such as the Lao People's Democratic Republic, the amounts of antimalarial drugs distributed through private pharmacies equal or exceed those distributed through government health programmes. Within the private sector, it is difficult to estimate the relative proportions sold through official pharmacies and through the informal sector by rural stores and street sellers, since many of the latter purchase their drugs at the official pharmacies.

The nongovernmental organizations and mission facilities also account for a considerable portion in many countries; for example, in Kenya they account for about 35% of drugs distributed. It appears that in most endemic countries about half of the antimalarial drugs are distributed through the public sector and half through the private sector.

7.3 Government purchases

Data exist at the country level, but rarely at the regional level, on the amounts purchased by government or public sources. For the private sector the data are usually not available or difficult to obtain. Where they exist, the data generally indicate only the total amounts of drugs purchased and not the purpose for which they are used —information that is important since the same drug may be used in different doses for different purposes, e.g., chloroquine may be used for radical or presumptive treatment, mass drug administration, or individual prophylaxis. A more precise measure of drug use is therefore required. A unit such as daily defined doses per 1000 inhabitants per day, as used in other drug utilization studies, would be useful for comparing patterns of drug use both within and between countries. Such patterns have changed with the transition of malaria programmes from a policy of eradication to one of control, in which drugs are provided more freely to the existing health institutions and to the health care workers in the periphery. Moreover, as a result of the general development of world trade, antimalarial drugs have become more easily available to those in need through commercial channels, even in rather remote areas.

WHO has conducted two surveys on the purchase and use of antimalarials. The first, in 1982, assembled information from 56

malarious countries of five WHO regions for 1978–79 and on their anticipated demand for 1980–84; this information was supplemented by estimates for the African Region (*3*). The second, conducted in 1985, gathered information on the period 1983–84 and the anticipated demand for 1985–89 in 84 malarious countries of the six WHO Regions.[1]

The amounts of drugs used, shown in Table 6, represent only a part of the true consumption. However, when the figures for one year are correlated with the number of cases of malaria reported for the same year, the amounts purchased are grossly in excess of those needed for the treatment of all reported cases. It appears also that the national requirements for antimalaria drugs (1985–89) are determined not so much by the actual need as by the previous year's purchases. In countries of the Americas and Asia with organized malaria control programmes, this excess in consumption is mainly due to the practice inherited from malaria eradication programmes of administering presumptive treatment to all fever cases, as well as to the mass drug administration practised in some countries for epidemic control. In the countries of tropical Africa whose national health services report drug consumption, there could be several explanations for this excess, including under-reporting of malaria cases, overdiagnosis, overprescription, repeated treatment with 4-aminoquinolines of drug-resistant malaria infections that fail to respond to the initial treatment, and indiscriminate dispensing of antimalarial drugs.

Whereas developing countries are usually considered to suffer from shortages in drug supply, in the case of antimalarials there is overconsumption.

7.4 Selection of the antimalarial drug to be used

Antimalarial drugs used in the health system should be of proven efficacy and safety, of good quality, and available at reasonable cost. Many countries, however, are unable to afford the cost of monitoring such parameters. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*4*), in which most of the Member States of WHO participate, could be used by countries that have no quality control

[1] KOUZNETSOV, R.L. *Trends in antimalarial drug consumption and requirements for antimalaria programmes in developing countries (1978–1989)* (unpublished WHO document WHO/MAL/88.1048).

Table 6. Antimalarial drugs for national antimalaria programmes within each of the six WHO regions: estimated consumption, 1978–79 and 1983–84, and estimated requirements, 1985–89 (expressed in kg of the base)

WHO region[a]	Drug	Quantity used				Estimated quantity required				
		1978	1979	1983	1984	1985	1986	1987	1988	1989
AFR	4-Amino-quinolines	131 800	131 800	101 783	158 681	151 143	135 749	157 232	190 924	59 985
AMR		5 271	5 956	6 334	8 534	12 537	10 869	7 895	7 408	–
SEAR		102 600	72 614	7 737[b]	9 911[b]	88 283	88 803	88 682	87 801	87 920
EUR[c]		4 343	3 615	1 285	1 880	2 000	2 200	2 000	1 800	1 600
EMR		7 057	14 826	11 713	13 568	14 279	15 439	15 030	15 391	17 472
WPR		13 981[d]	25 638[d]	46 087	42 308	38 855	40 026	39 165	37 104	34 414
Total		265 052	254 449	174 939	234 882	307 097	293 086	310 004	340 428	201 391
AFR	8-Amino-quinolines	–	–	54	134	134	99	99	70	10
AMR		201	215	282	409	509	556	375	352	–
SEAR		450	131	362[b]	432[b]	662	693	668	673	678
EUR[c]		175	265	40	30	35	40	35	30	30
EMR		73	88	63	67	74	83	85	93	93
WPR		162[d]	170[d]	5 847	3 265	1 113	994	878	770	686
Total		1 061	869	6 648	4 337	2 527	2 465	2 140	1 988	1 497
AFR	Tetrahydrofolate dehydrogenase inhibitors	–	–	282	261	263	158	154	111	66
AMR		27	36	32	17	22	22	23	20	–
SEAR		740	730	125	230	252	338	344	349	354
EUR[c]		543	469	250	270	300	300	270	250	250
EMR		326	446	249	218	317	338	319	294	291
WPR		179[d]	920[d]	5 212	1 715	4 914	4 883	4 845	4 700	4 585
Total		1 815	2 601	6 150	2 711	6 068	6 039	5 955	5 724	5 546
AFR	Sulfonamides and sulfones	–	–	194	232	1 218	1 239	1 930	970	375
AMR		75	98	234	317	385	382	402	323	–
SEAR		310	791	2 488	4 597	5 100	6 812	6 939	7 535	7 636
EMR		25	17	52	77	153	209	229	369	374
WPR		848[d]	1 663[d]	4 664	4 531	14 858	16 532	18 623	18 145	18 209
Total		1 258	2 569	7 632	9 754	21 714	25 174	28 123	27 342	26 594

Table 6 (continued)

WHO region[a]	Drug	Quantity used				Estimated quantity required				
		1978	1979	1983	1984	1985	1986	1987	1988	1989
AFR	Quinine	–	–	4 745	4 617	4 066	1 226	1 387	1 640	1 193
AMR		0	0	55	83	–	–	–	–	–
SEAR		–	2 286	25[b]	23[b]	197	231	231	231	231
EMR		0	0	5	6	7	67	190	282	315
WPR		4 224[d]	3 945	4 106	4 319	7 964	7 723	7 775	7 710	7 369
Total		4 224	6 231	8 936	9 048	12 234	9 247	9 583	9 863	9 108

[a] AFR = African Region; AMR = Region of the Americas; SEAR = South-East Asia Region; EUR = European Region; EMR = Eastern Mediterranean Region; WPR = Western Pacific Region.

[b] Excluding India, Myanmar, Thailand.

[c] Excluding Algeria and Morocco.

[d] Excluding China.

capability of their own by which to ensure the quality of the drugs they import. WHO should also be ready to assist countries that wish to establish quality control laboratories. In this regard, regional cooperation between small countries or those with limited resources should be fostered by WHO.

(See recommendation 9.7.2.)

7.4.1 *The public sector*

The first decision, whether to include a drug in the national formulary or the national essential drugs list and thereby select it for use in health facilities, is often made by a drugs committee or formulary committee, made up of clinicians and pharmacists, including the chief pharmacist in the country concerned. Such committees often refer to the criteria set out in the WHO Model List of Essential Drugs (*5*)—namely safety, efficacy, quality, stability, ease of storage, cost, and availability. The level of use of a drug will depend not only on the need for it but also upon many other factors, including its cost, its availability, and the cost of the staff, laboratory and diagnostic services and equipment needed to use it.

(See recommendation 9.7.5.)

It is possible to compare the clinical efficacy and the costs of various treatment regimens if the clinical cure rate of candidate treatments can be measured, the rate and severity of side-effects are known, and the costs of treatment and of disease can be calculated. One must also take into account the long-term epidemiological consequences of deploying alternative drugs, which, on the basis of present knowledge, cannot be predicted quantitatively. Such data on which to base firm decisions are seldom available or are of low quality. Thus, when the use of an expensive drug is being considered, the decision may be taken only on the basis of its cost.

There are two basic methods for determining the required amount of a specific drug. One is to refer to past consumption. This has the advantage that it relies for the most part on available data but the disadvantage that it reinforces existing prescribing patterns, which may be inappropriate and take no account of changing epidemiology. An alternative is the standard treatment/morbidity method, which uses available morbidity data and recommended standard treatment dosages to determine the quantities required for a given number of consultations. This has the advantage that it

provides an incentive to improve data collection by linking provisions of drugs to the data provided by health workers.

The latter method can also be used to estimate the emergency stocks needed to deal with epidemics, since by estimating the expected number of cases during an epidemic and specifying a standard treatment, it is possible to calculate the quantity of drug needed. Emergency stocks do not generally exist but they may be created in countries in which epidemics may be predicted to occur. Their composition will depend on which drugs in current use are effective for radical treatment. In addition, primaquine should be included, if reduction of transmission is envisaged, as may be the case in countries with areas that are nonmalarious but receptive to malaria. It is also necessary to ensure that the emergency stock is replaced regularly with fresh drugs so that the drugs do not become outdated. If internal transport difficulties are likely to delay delivery in an emergency situation, it is advisable to distribute the emergency stock to depots in vulnerable regions.

(See recommendation 9.7.3.)

If changes are made in recommended treatment regimens, this may have significant implications both for the budget and for the drug supply system. For example, a change in recommended treatment for malaria from 10 mg/kg chloroquine to 25 mg/kg effectively means that, unless additional drug supplies have been procured, existing supplies would only be sufficient to treat 40% of the patients treated previously. In addition, drug procurements often take a year or more to implement. The impact on the budget would be the most important since the cost of purchasing chloroquine would increase by 250%. If 10% of the overall drugs budget was previously spent on chloroquine, the total budget for drugs would have to be increased by 25% in real terms to provide enough drugs to treat the same number of cases. Clearly this would not be possible in many countries. Faced with such a situation, the health workers would have three options: provide complete treatment (25 mg/kg) for about 40% of the patients; provide complete treatment for some patients and send others to buy their chloroquine on the private market; or continue to provide 10 mg/kg to most of the patients despite the new recommendations.

Once the drugs are present in the country, it is often the chief pharmacist who allocates them to the health facilities that request them. He or she has to satisfy the competing demands, which makes

fair distribution very difficult. Typically, the specialists at the central hospital are geographically the closest as well as being politically powerful. Thus, these hospitals are usually given preference over rural health centres and dispensaries for the allocation of drugs. Transport is almost always a major problem, making it difficult to ensure timely deliveries to all health facilities, especially to those in remote areas. Other concerns are to prevent pilferage, to ensure that most of the drugs reach their destination, and to prevent deterioration due to poor storage conditions during transport. Recently, the production of counterfeit drugs has become an increasing problem in many countries.

7.4.2 *The private sector*

Patient demand rather than medical need is the major factor in the selection of drugs in the private sector. The private importer is likely to be more concerned with the relevance of the product as perceived by the clients, its price compared with alternatives, the income level of clients, and the degree to which the company has provided publicity and advertising for the product. The price of the product will not be of concern as long as the clients can afford it.

"Prescription only" drugs may be reserved for pharmacies with fully qualified staff, but in practice the designation "prescription only" may increase the client demand and make it more difficult to restrict its use, especially in countries which lack the resources to inspect pharmacies and drug sellers. The additional difficulty of obtaining a "prescription only" medicine may only increase its value (*6, 7*). The public's awareness of the existence of chloroquine-resistant malaria, which may be enhanced by private-sector advertising and by contact with pharmacy employees, may also increase the sale of newer antimalarials.

The private importer will base importations on the previous year's sales of a specific product, taking into account any price rises or special activities of the company that may increase demand and any new information about the incidence of drug-resistant malaria. The delivery times are likely to be much shorter than those in the public sector, so smaller quantities of drugs can be ordered more often. The private sector's distribution system is simple since the outlets are limited in number and concentrated in urban areas. The more remote and poorer urban areas are reached by the "informal" sector, which for the purposes of the "official" private sector acts like

other retail clients by providing its own transport and running its own affairs.

(See recommendation 9.7.4.)

7.5 User charges

Governments are increasingly asking their populations to pay for health services, drugs, or both. There has been a great debate as to whether people are prepared to pay for health care and whether user fees can be used to generate additional resources without discouraging appropriate use of health facilities. The joint UNICEF/WHO Bamako Initiative, in particular, aims to improve the quality of primary health care in sub-Saharan Africa by generating funds through the sale of essential drugs, including antimalarials (*8*).

If such user charges are well designed and affordable, they can improve and assist the rational use of drugs. However, there is a growing body of evidence to show that in certain circumstances user charges may have negative effects on malaria control. For instance:

(*a*) Utilization of health facilities by the cash-poor segments of the population, especially women and children, declines.[1]

(*b*) Self-medication from "unofficial" sources increases since these sources are willing to sell single tablets of drugs at a lower overall cost (*9*).

(*c*) Patients who continue to frequent health services demand better service, which in situations where the fee is unrelated to the drug consumption often results in the prescription of inappropriate amounts and forms of drugs. These drugs may then be hoarded for future use or may be sold to others for self-medication.[1]

(*d*) The people often cannot afford to pay for drugs at the times when they are most needed, e.g., farmers may be short of money during the rainy season when there is a higher incidence of malaria (*10, 11*).

As a result, the private unofficial sources of drugs, which are often located closer to people's homes than the government health services, take on a major role in drug distribution. This is particularly true in the more remote areas. The presence of a thriving "unofficial" drugs market and extensive self-medication may be indications that the public health services are geographically or

[1] *Financing essential drugs: report of a WHO workshop, Harare, Zimbabwe, 14–18 March 1988* (unpublished WHO document WHO/DAP/88.10).

financially inaccessible or of such low quality that they are not patronized. The disadvantages of self-medication with antimalarials are numerous. Nevertheless, it constitutes an important part of the health resources available within the community and is not likely to disappear in the foreseeable future. In fact, there are reasons to believe that it is on the increase (*9*).

(See recommendations 9.7.6 and 9.7.7.)

7.6 Prices and pricing policies

Antimalarial drugs can be classified into two price categories. The first might be termed "commodity generic" antimalarials, i.e., drugs that are traded in large quantities on the international market and whose patents have expired. The prime example is chloroquine. The other category comprises the newer antimalarials, which are available from only one or a few sources. These are still covered by patents and are therefore usually available only under brand names.

Table 7 shows, in United States dollars, the price per purchase unit of a number of antimalarial drug formulations available from international sources of supply. Calculating from that table and on the basis of the usual courses of treatment, the costs of a malaria treatment episode with some of these formulations are given in Table 8, for an adult weighing 60 kg. They vary enormously—from US $5.31 for treatment with halofantrine to 8 US cents (US $0.08) for treatment with chloroquine phosphate.

Raw materials account for about 70% of the price of a tablet of internationally traded bulk generic chloroquine. Bulk chloroquine phosphate has recently been trading on the international market for about US $30 per kg. Assuming 10% waste during formulation, 1 kg of chloroquine would yield about 6000 tablets of 150 mg base (or 9000 of 100 mg base); the active ingredient therefore costs about US $0.005 per tablet of 150 mg base. This works out to about US $5.00 per 1000 tablets of 150 mg base (or US $3.33 for 100 mg base) whereas the wholesale price of the generic form is about US $7.00 per 1000 tablets of 150 mg base. The additional 30% covers the costs of production, packaging and labelling, transport to the warehouse of the procurement service, a small profit for the generic manufacturer, and a small operating margin for the procurement service.

Raw materials account for only about 10% of the retail price of a brand-name antimalarial. Furthermore, a tablet of brand-name

Table 7. Current international prices (US $) of various antimalarial drugs[a]

Drug	Dosage form (unit)	Units per pack	WHO[b]	UNICEF[c]	IDA[d]	Lowest unit price
amodiaquine*	200 mg tab.	1 000	17.74		17.37	0.018
chloroquine phosphate	100 mg base tab.	1 000	6.05	5.94	6.43	0.006
chloroquine phosphate	150 mg base tab.	1 000	7.50	8.06	8.75	0.008
chloroquine phosphate	40 mg base/ml, in 5-ml amp.	100	5.40		5.83	0.054
chloroquine phosphate	50 mg/5 ml syrup in 1-litre bottle	1	1.85	1.65		1.65
doxycycline	100 mg tab.	1 000	28.65	42.47	27.86	0.028
halofantrine	250 mg tab.	6	5.31[e]			0.885
mefloquine	250 mg base tab.	1 000	481[e]			0.481
primaquine phosphate	15 mg base tab.	1 000	4.80	3.54	9.06	0.004
proguanil	100 mg tab.	1 000	20.16		22.92	0.020
quinine dihydrochloride	300 mg/ml in 2-ml amp.	100	13.25		14.69	0.133
quinine dihydrochloride	300 mg/ml in 2-ml amp.	10		1.52		0.152
quinine sulfate	200 mg tab.	1 000	26.20		23.65	0.024
quinine sulfate	300 mg tab.	100		3.49		0.035
sulfadoxine/ pyrimethamine	500 mg + 25 mg tab.	1 000	46.76	43.79	51.04	0.044
tetracycline	250 mg tab.	1 000	9.00	9.33	10.68	0.009

[a] Table updated by WHO Secretariat since the meeting of the Scientific Group. All prices in US $, FOB Europe; up to 25% should be added for shipping, handling, and insurance.
[b] WHO Supply Services, Geneva: prices at May 1990.
[c] UNICEF Supply Division, Copenhagen: Price List January 1990.
[d] International Dispensary Association, Amsterdam: Price Indicator May 1990 (conversion from Netherlands guilders at May 1990 rate).
[e] Price to WHO in January 1990.
* No longer recommended.

Table 8. Cost of one treatment episode for a 60-kg adult with some antimalarial drugs, calculated from Table 7

Drug	Dosage form (unit)	Lowest unit price (US $)	No. of units per treatment episode	Cost per treatment episode (US $)
halofantrine	250 mg tab.	0.885	6	5.31
mefloquine	250 mg tab.	0.481	4	1.92
quinine sulfate	200 mg tab.	0.024	63	1.51
quinine sulfate	300 mg tab.	0.035	42	1.47
quinine dihydrochloride	300 mg/ml in 2-ml amp.	0.133	7.5	0.99
amodiaquine[a]	200 mg tab.	0.018	8	0.14
sulfadoxine/pyrimethamine	500 mg + 25 mg tab.	0.044	3	0.13
chloroquine phosphate	100 mg base tab.	0.006	15	0.09
chloroquine phosphate	150 mg base tab.	0.008	10	0.08

[a] No longer recommended; see recommendation 9.3.1.

chloroquine may be about 6 times more expensive than the internationally traded generic equivalent. Some of this cost is accounted for by the difference in packing; the generic drug is packed

in tins of 1000 tablets, while the brand-name equivalent may be packed in blister packs or foil strips. Other elements of the cost of brand-name drugs are the costs of distribution, promotion and advertising, and research and development.

Drug importation policies vary considerably from one country to another, according to the degree to which the government intervenes to hold drug prices down. For example, for the most part the governments do not intervene in Africa south of the Sahara, whereas in Algeria and Tunisia the governments purchase generic formulations through international competitive bidding or by negotiations with companies. As a result, drugs in these two countries are only half as expensive as in France, whereas in French-speaking Africa, south of the Sahara, prices are on average 12–28% higher than in France.[1]

(See recommendations 9.7.8–9.7.11.)

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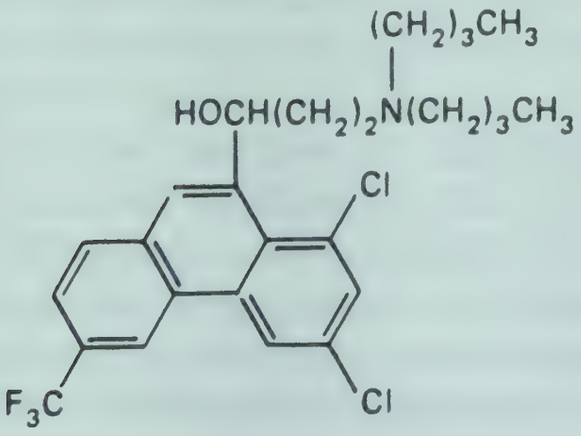
8. NEW DRUGS

8.1 Halofantrine

Halofantrine (Fig. 1), a phenanthrenemethanol, was registered for the treatment of malarial infections in 1988 in France and some French-speaking African countries. Its registration is being sought worldwide. The drug is marketed as tablets containing 250 mg halofantrine hydrochloride (233 mg base) and as a suspension containing 100 mg hydrochloride (93 mg base) in 5 ml. The manufacturers recommend the treatment dose for adults as two 250-mg tablets given 3 times at 6-hour intervals. The dose for children is 8 mg/kg of body weight in 3 doses at 6-hour intervals. It is a blood schizontocide with an activity comparable to that of mefloquine in a variety of laboratory models (*1*, *2*). It appears to have activity against some but not all mefloquine-resistant isolates in these models.

Fig. 1. Halofantrine



Toxicological screening has provided no evidence of genotoxic or teratogenic activity, or of adverse effects on fertility or fecundity (*3*). It was found, however, to be embryotoxic at doses of 30 mg base/kg per day in rats and 60 mg base/kg per day in rabbits over a period of 4 weeks. Dose-related reductions in growth rate and survival of pups occurred when they were exposed to milk from dams given 50 mg base/kg per day but such an effect was not observed at 25 mg

base/kg per day. The manufacturers indicate that use of the drug is contraindicated for pregnant women and lactating mothers.

Halofantrine is largely insoluble in water. Its systemic absorption from the currently available tablet and suspension formulations varies unpredictably, but the variations are reduced when the dosage is divided. These observations suggest that the formulations have poor bioavailability and continued efforts are needed to develop both an improved oral dosage form and an injectable solution.

The clinical and parasitological response to halofantrine has been evaluated in almost 1000 patients with acute falciparum or vivax infections. These studies have provided evidence that halofantrine can produce clinical and parasitological cures of infections resistant to chloroquine and to pyrimethamine/sulfadoxine combinations (*4, 5*). Early studies *in vitro* also indicated that halofantrine was active against isolates and clones of *P. falciparum* with reduced susceptibility to mefloquine (*4*). However, more recent data indicate that this absence of cross-resistance may not be absolute. Webster et al. (*6*) reported that mefloquine-resistant clones of *P. falciparum* isolated from a mefloquine treatment failure in Thailand were not susceptible to halofantrine.

In addition, the chloroquine-sensitive Sierra Leone D-6 clone of *P. falciparum* has consistently shown over a period of 3 years a parallel low sensitivity to mefloquine and halofantrine (IC_{50} for halofantrine 3.94 ng/ml and IC_{50} for mefloquine 7.26 ng/ml) compared to the chloroquine-resistant Indochina W-2 clone, which is sensitive to both drugs (IC_{50} for halofantrine 0.39 ng/ml and IC_{50} for mefloquine 1.31 ng/ml) (*7*). Cross-resistance between halofantrine and mefloquine, as well as between halofantrine and chloroquine, quinine and primaquine, has been observed in rodent malaria models (*8, 9*). The relevance of these laboratory findings to the clinical situation is unclear and cannot be resolved until halofantrine is used in controlled clinical studies to treat infections that have failed to respond to mefloquine. In the initial field trial of halofantrine in Thailand, 3 of 14 recrudescent patients showed evidence of cross-resistance to mefloquine.

Halofantrine appears to be a safe and well tolerated drug. Abdominal pain, diarrhoea, pruritus, and skin rash have been reported following its administration as well as an occasional elevation of serum transaminase. The relationship of this last observation to medication is unclear, but values have usually returned to normal within a week after treatment. Significant effects

on cardiovascular, respiratory, and autonomic nervous function, humoral and cellular immune mechanisms, and antifolate activity have not been observed in animals.

8.1.1 *Pharmacokinetics*

Halofantrine and its active *N*-desbutyl metabolite can be determined in biological fluids by high-performance liquid chromatography (HPLC) with ultraviolet detection (*10*) or fluorescence (*11*).

Studies on healthy volunteers showed that the drug was absorbed slowly, reaching peak levels about 6 hours after dosing. The bioavailability parameters of area under the plasma-concentration/time curve (AUC) and maximum observed plasma concentration (C_{max}) did not increase consistently with dose at the dose levels evaluated, suggesting incomplete or erratic absorption (*12*). Peak levels of the *N*-butyl metabolite occur about 12 hours after administration of a single dose. The estimated elimination half-life of the metabolite is about 3 days, compared with 1 day for halofantrine. The limited pharmacokinetic data available indicate wide intersubject variability in the extent of absorption of halofantrine although the time to maximum plasma concentration appears consistently to be about 6 hours.

There is evidence that the bioavailability of halofantrine is increased if the drug is given with a fatty meal (*13*), probably owing to its lipid solubility. This effect has been seen with both single and multiple doses.

Irregular absorption and variable peak levels are likely to affect the clinical effectiveness of halofantrine. In a study in Thailand, serum levels of halofantrine and its *N*-desbutyl metabolite were measured in 14 patients who developed recrudescences of falciparum malaria and in 63 patients who were cured by treatment (*5*). The patients received either 1000 mg of halofantrine as an initial dose followed by 500 mg 6 hours later, or 500 mg every 6 hours for 3 doses. The serum levels of halofantrine plus its *N*-desbutyl metabolite and of the metabolite alone were both significantly higher in the cured patients than in those in whom treatment failed. The mean day-3 serum level of halofantrine in patients with recrudescences was approximately half that of the cured patients. The results from this study also indicated a wide individual variation in drug absorption.

8.1.2 *Clinical and field studies*

Trials using several formulations of halofantrine—capsules, tablets, and flavoured suspensions for children—have been carried out in French Guiana, Gabon, Kenya, Malawi, Mali, Pakistan, the Solomon Islands, and Thailand and also on infected travellers arriving in France (*14*). The commonest side-effects were diarrhoea, cough, abdominal pain, nausea, vomiting, dizziness, headache, and pruritus.

A 5% suspension was less effective than the tablet preparation, a cure rate of 84% being obtained with the suspension compared with 97% with the tablet formulation in individuals followed for 28 days. Higher cure rates have been obtained in preliminary studies with a 2% suspension given as 8 mg/kg of body weight in 3 doses than with the 5% suspension given at the same dosage. The efficacy was equivalent in patients infected with chloroquine-sensitive or resistant parasites. Pharmacokinetic studies have suggested an 18% lower bioavailability with the 5% suspension than with the tablet or capsule formulation. The drug was less effective in children under 5 years of age than in patients over 12 years of age; the reasons for this are not clear.

Halofantrine is a promising compound for the treatment of chloroquine-resistant falciparum malaria. The bioavailability of existing formulations is highly variable and raises concern that subtherapeutic blood concentrations might encourage the selection of resistant parasites and that high, toxic levels could be attained in some subjects. A more reliable formulation of halofantrine is needed as well as a policy which defines its optimal use to retain its efficacy. Particularly, information on its efficacy against mefloquine-resistant infections is required.

(See recommendation 9.8.1.)

8.2 Chloroquine combinations to "reverse" resistance

Recent studies have shown that resistance to chloroquine results from the active transport of the drug out of the parasitized red cell so that toxic levels do not build up in the parasite's cytoplasm (*15, 16*). Verapamil and two other calcium-channel blockers, as well as vinblastine and daunorubicin, all slowed the release and increased the accumulation of chloroquine by chloroquine-resistant but not susceptible *P. falciparum in vitro*.

"Reversal" of chloroquine resistance by such compounds has also been demonstrated *in vivo*. Preliminary results have shown that, in primary blood-induced infections with the multidrug-resistant Viet Nam Smith strain of *P. falciparum* in *Aotus* monkeys, treatment with nifedipine at 5, 10, or 20 mg/kg of body weight plus chloroquine at 20 mg/kg administered orally for 3 days initially suppressed parasitaemia. However, re-treatment with nifedipine (20 mg/kg) plus chloroquine (20 or 40 mg/kg) was required before 3 out of 4 monkeys were cured; the fourth died of possible drug toxicity.

SKF 21133A, a chlorpromazine analogue without typical dopamine-receptor side-effects, when given with chloroquine also resulted in initial suppression of chloroquine-resistant *P. falciparum* and parasite clearance in monkeys upon re-treatment. The regimen was not, however, curative. More recently desipramine, a tricyclic antidepressant, has been shown to have superior "reversal" properties to verapamil and to be effective *in vitro* at concentrations that are easily obtained with doses used in humans for the treatment of depression. Parasitaemia in *Aotus* monkeys infected with chloroquine-resistant *P. falciparum* was rapidly suppressed by chloroquine plus desipramine. Desipramine was found to be one of the most effective compounds yet described for the "reversal" of chloroquine resistance, both *in vitro* and *in vivo* (*17*).

Not only have these observations strengthened scientific evidence for a mechanism of resistance to chloroquine, they have also stimulated several groups to consider using chloroquine in combination with calcium antagonists for the treatment of chloroquine-resistant malaria infections. This should be viewed with cautious optimism since many questions remain to be answered before such combinations are tested in patients. For example, while several compounds with apparent lack of cardiotoxicity have been shown to "reverse" resistance to chloroquine in *P. falciparum* (*18*), detailed pharmacokinetic and toxicological studies must be conducted on these compounds alone, as well as in combination with chloroquine, before clinical evaluation can be considered. Desipramine produces arrhythmias at doses above its therapeutic range as an antidepressant, and chloroquine shows cardiotoxicity at high doses; a combination of the drugs might have increased toxicity, even at low doses. Such drug interactions may be important, particularly since chloroquine may accumulate in the host to a greater extent in the presence of such compounds, thereby reducing the therapeutic index of chloroquine itself.

In contrast, calcium agonists enhanced efflux of calcium and actually increased "resistance" to chloroquine. These findings, combined with previous unconfirmed clinical malaria in patients undergoing chloroquine prophylaxis and phenytoin therapy, suggest that this drug interaction may have significant clinical relevance (*19*).

Verapamil, chlorpromazine and several other calcium antagonists, which "reverse" resistance to chloroquine, do not "reverse" resistance to mefloquine. However, one calcium antagonist, WR 256,473, was found to potentiate *in vitro* the action of mefloquine against mefloquine-resistant isolates and clones of *P. falciparum* without affecting the response of sensitive parasites (*20*).

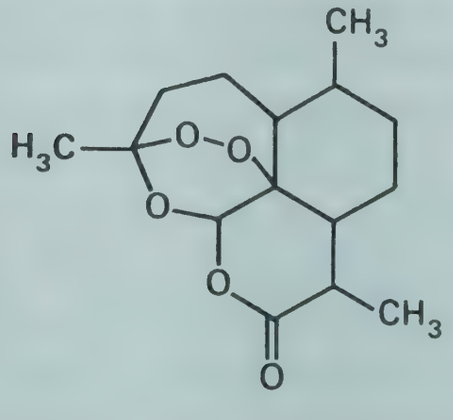
8.3 Artemisinin and its derivatives (*21*, *22*)

8.3.1 *Preclinical studies*

Artemisinin is the antimalarial principal isolated by Chinese scientists in 1972 from *Artemisia annua* L., a medicinal plant from which is derived the traditional medicine qinghaosu. According to surveys, *A. annua* indigenous to China yielded 0.01–0.6% (w/w) artemisinin from air-dried plants. The yields varied with the location and the time of collection. Leaves and flowering tops produced the highest yields.

Artemisinin is a sesquiterpene lactone with an unusual peroxide linkage. Its absolute configuration was resolved by X-ray diffraction studies (Fig. 2). It has marked activity against malaria parasites, including multidrug-resistant isolates of *P. falciparum*. The peroxide moiety of the molecule appears to be responsible for the antimalarial activity.

Fig. 2. Artemisinin



Artemisinin is poorly soluble in water and in oils; this has stimulated studies to increase its solubility in both types of solvent by the synthesis of appropriate derivatives. Derivatives of artemisinin, however, appear to be more unstable than the parent compound. Both artemether (Fig. 3) and sodium artesunate (Fig. 4) are susceptible to moist and acidic conditions and the usefulness of sodium artesunate as an intravenous formulation is impaired by its poor stability in aqueous solutions.[1] Consequently, Lin et al. (*23*) synthesized a new series of water-soluble derivatives, of which artelinic acid (Fig. 5) was shown to have a higher activity *in vivo* against *P. berghei* than either artemisinin or artesunate. More recently Li Ying and her colleagues at the Shanghai Institute of

Fig. 3. Artemether

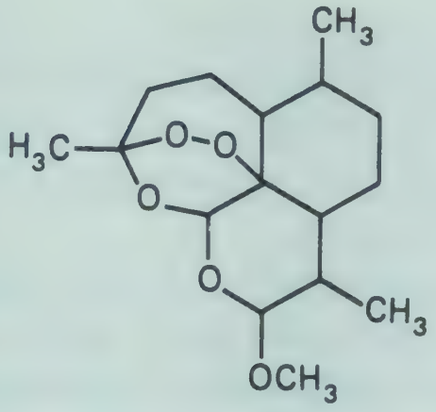
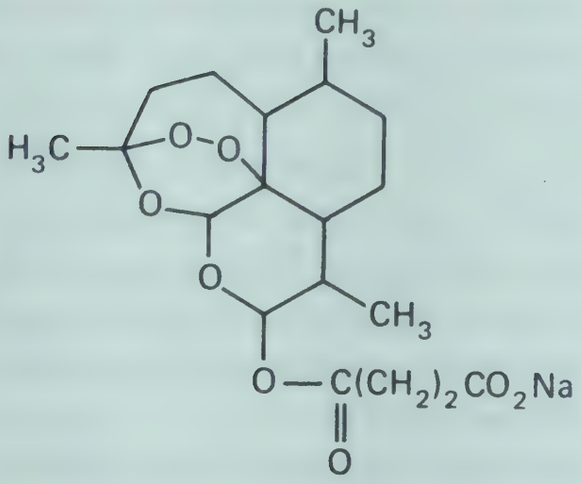
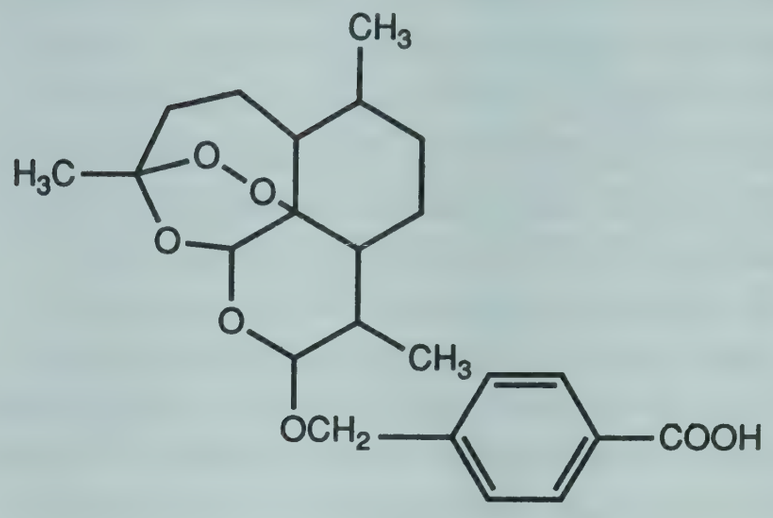


Fig. 4. Sodium artesunate



[1] *The development of artemisinin and its derivatives*: report of a meeting of the Scientific Working Group on the Chemotherapy of Malaria (unpublished WHO document TDR/CHEMAL/ART/86.3).

Fig. 5. Artelinic acid



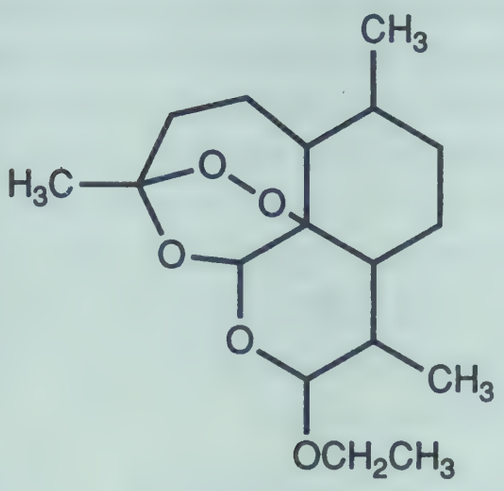
Materia Medica (personal communication) have synthesized other water-soluble artemisinin derivatives, which are reported to have an efficacy either equivalent to or greater than artelinic acid against the RC strain of *P. berghei*.

While water-soluble derivatives have potential for inclusion in intravenous formulations, oil-soluble derivatives may have application as intramuscular injectable formulations for use as life-saving drugs at the peripheral parts of the health service. Artemether, the oil-soluble methyl ether derivative of artemisinin, has been studied widely in China and was registered in that country in 1987 as an antimalarial.

Arteether (Fig. 6), the ethyl ether derivative, has been developed by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (*24*). Arteether is a crystalline, stable, and highly lipophilic compound. It is 2–3 times more active than artemisinin against both the drug-sensitive Sierra Leone D-6 and the drug-resistant Indochina W-2 clones of *P. falciparum*. There is, however, no significant difference in the activities of arteether, its alpha-epimer, or artemether either against these clones or against rodent malaria parasites *in vivo*.

Acute toxicity studies indicate that artemisinin, artemether, arteether, and artesunate have higher LD_{50}s and chemotherapeutic indices than chloroquine. Subacute toxicity studies are incomplete. The toxic effect of artemisinin and its derivatives was mainly manifested in the haematopoietic cells of the bone-marrow,

Fig. 6. Arteether



especially those of the erythroid series. Cardiotoxicity has also been described following the administration of artemisinin, artemether, and artesunate at high doses to rats, dogs, or monkeys. Murine bone-marrow polychromatic erythrocyte micronucleus and Ames tests have both failed to reveal any mutagenic activity of artemisinin or any of its derivatives. However, teratogenic studies in mice and rats indicate that all these drugs exhibit fetal toxicity even at relatively low doses of 1/200–1/400 of the LD_{50}. Both death and absorption of the fetus were observed.

8.3.2 *New dosage forms and clinical experience*

8.3.2.1 *Artemisinin suppository.* A suppository formulation has been developed in China from micronized artemisinin and a water-soluble matrix with Tween-80 added as suspending agent. Owing to the physical state of artemisinin in the preparation, the suppository serves as a sustained-release dosage form. When given to healthy volunteers in a single suppository dose of 10 mg/kg of body weight, the plasma drug concentrations were shown to fit essentially a one-compartment open model. This formulation has been used in field trials conducted between 1982 and 1984 in China (Shen Jiaxiang, personal communication), the dose regimen being 2.8 g administered over 3 days with supplementary doses of nitroquine and dapsone (0.125 g each) given on the 4th day for infections with *P. falciparum*. Among the 416 cases treated, 358 cases were *P. falciparum* infections, including 14 cerebral and 18 other severe cases. Clinical

cure was obtained in 355 cases, the time required for subsidence of fever being 15–39 hours and for parasite clearance 36–53 hours. Only 1 of the 3 cases that were not cured died of complications, the other 2 had diarrhoea which necessitated a change in their course of treatment. All but one of the cerebral and severe infections were cured. However, the recrudescence rate in 83 cases followed for 4 weeks after therapy was as high as 45.8%. When the therapy was prolonged for 7 days, the failure rate was reduced to 5–6%, and in 69 cases also treated with nitroquine and dapsone, the rate was further reduced to 1.5%.

8.3.2.2 *Artemether.* A formulation of artemether for intramuscular injection is available in China. It has been used in a dosage regimen of 480–600 mg given over a 3–5-day period for a patient of 50 kg body weight. It was noteworthy that subsidence of fever and clearance of parasitaemia were independent of the dosage, although radical cure rates did correlate with higher doses. It was estimated that a 480-mg dose of artemether was similar in therapeutic efficacy to 900 mg of artemisinin in oil solution or suspension. When artemether was injected intramuscularly into healthy volunteers in a single dose of either 6 or 10 mg/kg of body weight, the peak drug concentrations were 0.145 ± 0.038 and 0.224 ± 0.026 mg/ml respectively; the times to reach the peak were 5.24 ± 1.30 and 6.27 ± 2.57 hours, respectively (Shen Jiaxiang, personal communication).

During 1982–86, 307 cases were treated in Hainan Island and Yunnan Province with 480 mg artemether given over 5 days. The 253 patients followed up were all clinically cured, with a recrudescence rate of 6.7% observed after 28 days. Thirteen were critically ill, including 7 with cerebral malaria, 1 with serious hepatic and renal impairment, 1 with gastrointestinal tract haemorrhage, and 1 with diarrhoea. The time for clearance of fever was 21.1–29.7 hours and for parasite clearance 31.9–76.2 hours. Untoward effects included transient elevation of body temperature after subsidence of fever, marginal reduction of reticulocyte counts, and short-term bradycardia. All patients recovered from these side-effects without additional treatment (Shen Jiaxiang, personal communication).

8.3.2.2 *Treatment with artesunate.*

(*a*) *Dual pack sodium artesunate for injection.* Injectable sodium artesunate was developed in China to overcome the instability of

sodium artesunate in water. The pack consists of two ampoules: one contains 60 mg of sterile anhydrous artesunic acid in powder form, and the other contains 0.6 ml of sodium bicarbonate solution for injection. The solution is prepared just before use and injected with 5.4 ml of dextrose solution or dextrose in saline to make up the volume to approximately 6 ml.

Pharmacokinetic studies in healthy volunteers given a single dose of sodium artesunate showed that the drug concentration in the blood fitted a two-compartment model. The average elimination half-life of artesunate was 23 minutes, and that of its active metabolite, dihydroartemisinin, was 45 minutes. A comparative study of artesunate and quinine dihydrochloride carried out on 60 cases of uncomplicated falciparum malaria claimed that the time to achieve parasite clearance was significantly shorter with artesunate (Shen Jiaxiang, personal communication).

Altogether 346 cases were treated with intravenous artesunate during 1985–86. These included 258 cases of uncomplicated falciparum malaria, 33 cerebral cases, and 55 cases of vivax malaria. All patients were rapidly cured clinically. The time required for fever subsidence was 16–25 hours and for parasitaemia clearance 34–56 hours in the 258 cases of uncomplicated falciparum malaria. No adverse reactions were observed. The recrudescence rate was 49.4% in a 28-day follow-up of 89 patients given a total dose of 240 mg over 3 days; it was reduced to 5.6% when a total dose of 480 mg was given over 7 days. Thirty-one of the 33 cerebral cases were successfully treated with the regimen, the mean time for return to consciousness being 29 hours. Fever clearance was obtained after 30 hours and parasite clearance after 55 hours in these patients. In the treatment of vivax cases, the fever subsidence time was 9.9 hours, and the parasitaemia clearance time was 44.7 hours. The recrudescence rate was 53.5% following the administration of 240 mg over a 3-day period (Shen Jiaxiang, personal communication).

(*b*) *Oral formulation of artesunate*. Preliminary studies in Thailand indicated that artesunate administered orally as tablets was highly effective in parasite and fever clearance in the treatment of uncomplicated falciparum malaria. There were no gastrointestinal or neurological side-effects, but peripheral polymorphonuclear leukocyte counts were reduced in all patients (T. Harinasuta & D. Bunnag, personal communication).

8.3.3 *Operational implications*

Artemisinin, artemether, and artesunate have been used to treat thousands of patients with falciparum malaria in China. The results indicate a rapid initial clearance of parasitaemia, possibly faster than with any other drug, a lack of serious toxicity and, in studies of severe falciparum malaria, exceptional efficacy. These drugs clearly show promise for reducing the high mortality of severe falciparum malaria (20% in strictly defined cerebral malaria). Unfortunately, a lack of adequate toxicity assessment has delayed access to these exciting drugs outside China. The English translations of the Chinese registration documentation on artemether and artesunate, which are now available, should facilitate the completion of the toxicity studies within the next year. A protocol for the clinical assessment of these drugs in severe falciparum malaria is being prepared by WHO and will be available for the guidance of suitable trial centres. There is an urgent need to build on the extensive Chinese experience and to define which compounds, formulations, routes of administration, and dosage regimens can, in the future, be recommended for the treatment of particular groups of patients with falciparum malaria.

(See recommendations 9.8.2–9.8.4.)

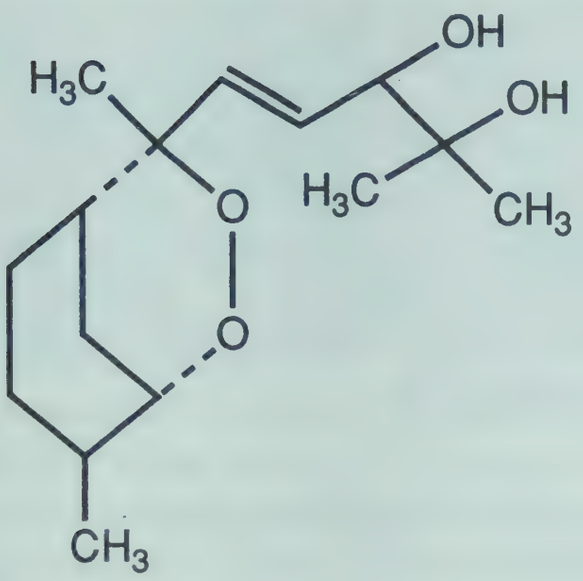
8.4 Trioxanes, tetraoxanes, and peroxides

As the antimalarial activity of artemisinin and its derivatives appears to be related to the 1,2,4-trioxane ring, attempts have been made to synthesize simple trioxanes which may lead to potential antimalarial compounds. Over 200 such trioxanes and tetraoxanes have been synthesized by Jefford and his colleagues, some of which have activity *in vitro* against drug-resistant (Indochina W-2) and drug-sensitive (Sierra Leone D-6) clones of *P. falciparum* (*25*).[1] Preliminary studies indicate that certain of these compounds have antimalarial activities *in vivo* against rodent malaria parasites (C. Jefford & W. Peters, personal communication).

The demonstration of antimalarial activity of the sesquiterpene peroxide, yingzhaosu A (Fig. 7) from *Artabotrys uncinatus* (*26*), has also led to the synthesis of analogues of this compound, particularly

[1] *The development of artemisinin and its derivatives*: report of a meeting of the Scientific Working Group on the Chemotherapy of Malaria (unpublished WHO document TDR/CHEMAL/ART/86.3).

Fig. 7. Yingzhaosu A



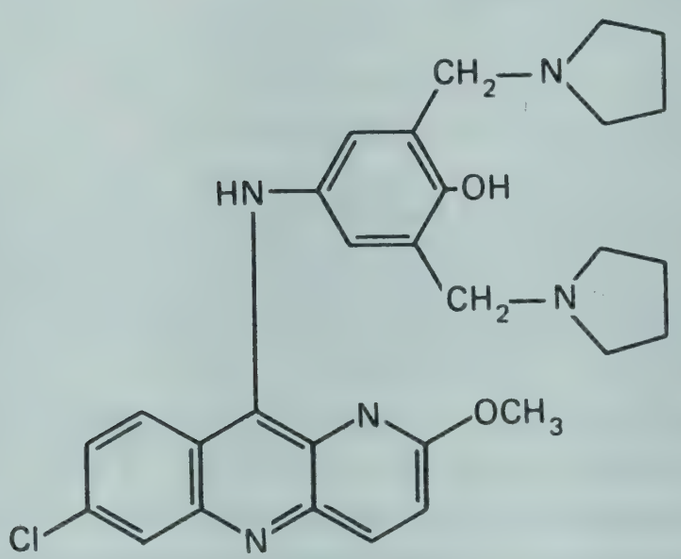
since the parent compound is difficult to isolate. Hofheinz et al. (*27*) have devised a method for the synthesis, starting from carvone, of derivatives of the 2,3-dioxabicyclic nonane ring structure which is the core structure of yingzhaosu A. Most of the compounds were active and three have been selected for preclinical development (Ro 40-6772, Ro 41-3823, and Ro 42-1611). These compounds have extremely low acute toxicity in mice and rats, with an LD_{50} of over 3000 mg/kg, and show no mutagenic potential in the Ames test. Their activities *in vitro* against *P. falciparum* are comparable to those of mefloquine and quinine, but they are 5–10 times less active than artemisinin. They are also active *in vivo* against rodent malaria models, greater activity being observed via the parenteral than the oral route.

In vivo studies in rodent models indicate that Ro 42-1611 shows an apparent lack of cross-resistance with chloroquine, mefloquine and quinine and only a moderate level of cross-resistance with artemisinin. In contrast, Ro 40-6772 shows a high level of cross-resistance with artemisinin, and Ro 41-3823 shows moderate cross-resistance with chloroquine and artemisinin. All three antagonize the action of chloroquine but are additive in their action when combined with mefloquine or artemisinin. These compounds have potential for clinical development and may be useful for the treatment of severe malaria since they appear to be rapidly acting schizontocides.

8.5 Mannich bases

Pyronaridine, a mannich base (Fig. 8), was synthesized in 1970 at the Institute for Parasitic Diseases, Shanghai (*28*). The compound exhibits marked blood schizontocidal activity against both rodent and simian malarias. It has been shown to be active against chloroquine-resistant *P. berghei* parasites *in vivo*. Its activity against a chloroquine-sensitive isolate of *P. berghei* was approximately 5 times that of chloroquine. It apparently has no action against tissue stages of *P. cynomolgi* (*29*).

Fig. 8. Pyronaridine



Acute toxicity studies in mice demonstrated an LD_{50} of 1368 mg/kg of body weight after oral administration and 251 mg/kg following intramuscular administration, indicating a poor bioavailability by the oral route. The corresponding values for chloroquine were 663 and 90 mg/kg respectively. Subacute toxicity studies have been conducted in rats, rabbits, and dogs. Studies with rats given 20 mg/kg intragastrically for 14 days failed to elicit any major side-effects. Rabbits given 10 mg/kg for 7 days intravenously also tolerated the drug well. However, dogs given 12 mg/kg intragastrically daily for one month died within 30 days after medication following loss of appetite, salivation, vomiting, and trembling; one of these dogs showed serious heart failure before death (*28*).

Mutagenicity tests with the *Salmonella typhimurium*/microsome system indicated mutation without metabolic activation in strain TA

1537. Reversion was dose-dependent and similar to chloroquine. There was no induction of mutation in other strains (*30*).

Teratogenicity tests in rats conducted with the equivalent of 8, 15, 30, or 33 times the clinical dose yielded no evidence of teratogenic effects, but the rate of fetal resorption was significantly increased (*31*). It is not clear if such an observation would preclude the widespread use of the drug in women of childbearing age. The significance of embryotoxicity in rats cannot be predicted without studies in another animal species.

Resistance to pyronaridine could be induced through increasing subcurative doses of the drug in the *P. berghei* model. Within 23 passages, it reached a very high level, with refractoriness to a dose of 2400 mg/kg. The virulence of the pyronaridine-resistant isolate was much reduced. The isolate also showed reduced sensitivity to mepacrine, 4-aminoquinolines, and artemisinin. When drug pressure was removed, the pyronaridine-resistant line reverted to pyronaridine sensitivity within 5 passages (*32*).

Pyronaridine was also independently tested by the Walter Reed Army Institute of Research, Washington, DC, USA. It was curative against a chloroquine-resistant strain of *P. berghei* in mice in a schizontocidal test at doses of 20–640 mg/kg, with toxicity observed at the highest dose. It was effective in a parasitaemia-suppression test against both chloroquine-sensitive and resistant strains of *P. berghei*, although the 90% suppression doses (SD_{90}) were slightly higher with the resistant strain. It showed similar activity against the sensitive and resistant clones of *P. falciparum in vitro*. Thus, the drug does not appear to show cross-resistance with chloroquine.

Pharmacokinetic studies in rabbits and man have shown an elimination half-life of about 60 hours, but this might be longer since the analytical limit of sensitivity was about 10 mg/ml and the study in humans was only conducted for 72 hours.

Pyronaridine has been used since 1970 in China to treat human falciparum malaria. It is available as oral and as injectable intramuscular and intravenous formulations. Doses of 1.2–1.6 g given over 2–3 days cured infections due to both chloroquine-sensitive and resistant parasites (*33*; Shao Baoruo, personal communication). All patients tolerated the therapeutic dosages of pyronaridine well, the main adverse reactions of the oral formulation being headache, dizziness, gastrointestinal disorders, and transient electrocardiographic changes. Although there was local irritation at the injection site with the intramuscular for-

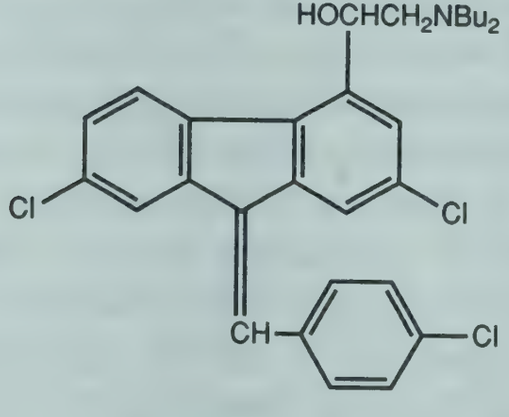
mulation, no other side-effects were observed with either this or the intravenous formulation.

Pyronaridine is structurally very similar to amodiaquine and so it must be determined whether the two drugs share similar bone marrow toxicity. Pyronaridine may, however, have a different mode of action and toxicity from amodiaquine or chloroquine by virtue of the extra nitrogen atom in the ring structure. This can be clarified by selective screening of pyronaridine and certain of its analogues that have been synthesized.

8.6 Benflumetol[1]

Benflumetol (Fig. 9) was synthesized in the 1970s by the Academy of Military Medical Sciences, Beijing, and registered for use in China as an antimalarial drug in 1987. The compound is poorly soluble in water and oils but is soluble in unsaturated fatty acids such as oleic and linoleic acid. It is formulated for oral administration as a solution in linoleic acid.

Fig. 9. Benflumetol



Preclinical efficacy studies showed that benflumetol had an ED_{50} and an ED_{90} of 1.02 mg/kg per day and 2.05 mg/kg per day respectively against the N strain of *P. berghei* in mice, and could cure *P. cynomolgi* and *P. knowlesi* infections in rhesus monkeys, the minimum curative doses being 48 mg/kg per day and 12 mg/kg per day respectively. Little is known about cross-resistance with other drugs.

[1] This section is based on information made available to the Scientific Working Group on the Chemotherapy of Malaria of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, at its April 1989 meeting in Beijing.

Acute toxicity studies have been carried out in mice, rats, and dogs but no deaths were observed in any species following oral administration. This is probably due to the drug's poor oral availability, which was also indicated by the large amounts remaining in the gastrointestinal tract 24 hours after oral dosing and the fact that it was mainly eliminated in the faeces. Subacute toxicity studies in rats and dogs indicated few toxic effects. Atrophic degeneration of the kidney glomerulus and liver degeneration were observed in dogs given 480 mg/kg per day for 28 days but these changes were reversible on withdrawal of the drug. Similar changes were observed in rats after 13 weeks of drug administration. Slight haematopoietic and calcium depression and increases in leukocyte counts were also observed in rats. These changes were also reversible. Benflumetol was not mutagenic, teratogenic, or photo-toxic and it did not affect reproduction in rats.

When it was absorbed, benflumetol was distributed in the tissues rapidly and widely. Peak plasma concentrations were reached in 8 hours. Elimination was slow, the biological half-life exceeding 78 hours in mice. The drug is highly protein-bound.

Clinical studies using benflumetol as capsules, each containing 100 mg base in linoleic acid, have been carried out in China since 1979. A phase I pharmacokinetic study in human volunteers given a single oral dose of 800 mg showed peak plasma levels at 48 hours, after which the drug concentration decreased slowly and was still detectable after 150 hours. The pharmacokinetics appeared to fit a two-compartment model with half-lives $t_{1/2(\alpha)}$ and $t_{1/2(\beta)}$ of 1.64 hours and 47.42 hours respectively. There was, however, marked variation in the pharmacokinetic parameters, indicating poor bioavailability. Limited dose-finding studies indicated that 2000 mg of benflumetol given over 4 days (800 mg on day 0 and 400 mg daily on days 1–3) cured *P. falciparum* infections in 20 out of 20 patients in Yunnan Province and in 18 out of 20 patients in Hainan Island. Studies in 314 patients from these localities gave cure rates above 96%, with fever subsidence in 38–41 hours and parasite clearance in 62–67 hours.

Benflumetol is now being administered orally in China together with artemether for the treatment of *P. falciparum* infections. Preclinical studies have shown that such a combination is synergistic, the optimum ratio of benflumetol to artemether being 2.7:1 against *P. berghei* and 6:1 against *P. knowlesi*. On the basis of the results obtained in the *P. knowlesi*/rhesus monkey model, a dose

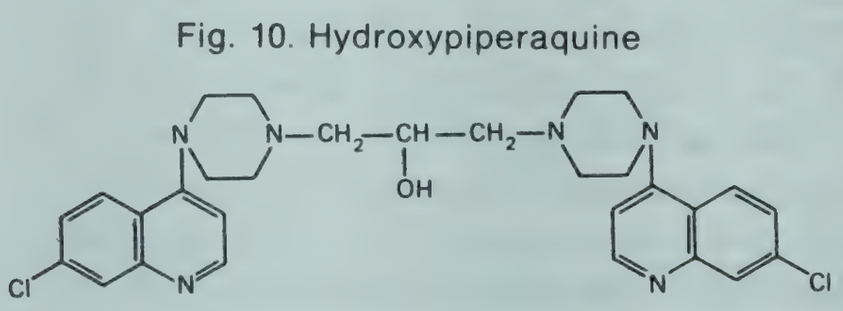
regimen of 160 mg artemether plus 960 mg benflumetol on the firs day, followed by 80 mg artemether plus 480 mg benflumetol on the next 2 days is now used for the treatment of human infections. A cure rate of 92.5% has been reported in 40 patients suffering from falciparum malaria, with fever clearance and parasite clearance times of 25.3 ± 7.0 hours and 42.5 ± 7.6 hours, respectively.

8.7 Hydroxypiperaquine

Interest in the development of piperaquine and its analogues waned when field studies failed to show any major advantages over chloroquine, but more recently, following a series of studies in China, interest in these compounds has increased.

Hydroxypiperaquine (Fig. 10) was synthesized in China. The acute, subacute and chronic toxicity in mice, dogs, rabbits, and monkeys is less than that of chloroquine. The drug has no apparent mutagenic, teratogenic, or embryotoxic activity. In *P. berghei*-infected mice and *P. cynomolgi*-infected monkeys treated with this compound, the onset of parasite clearance was slower than with chloroquine but there was no marked difference in the absolute clearance time (*34*). However, recrudescences were more frequent in monkeys treated with hydroxypiperaquine than in those given chloroquine. Chloroquine-resistant *P. berghei* was almost as sensitive to hydroxypiperaquine as the chloroquine-sensitive isolate.

Fig. 10. Hydroxypiperaquine



In clinical trials in Yunnan Province, in areas with a moderate frequency of chloroquine-resistant falciparum malaria, fever and parasite clearance occurred within 28 hours and 50 hours respectively in all 93 cases studied. Only one of 60 cases observed for 4 weeks showed recrudescence. The drug was administered orally at a total adult dose of 1.5 g base over 3 days (600 mg on days 0 and 1 and 300 mg on day 2). Chloroquine in the same regimen failed to produce parasite clearance within 7 days in 7 out of 28 cases (RII and

RIII); follow-up of 19 others showed 5 recrudescences (RI). Parasite and fever clearance among the S and RI cases were slower than with hydroxypiperaquine (68 and 42 hours respectively), and hydroxypiperaquine was better tolerated than chloroquine (*35*).

In Hainan Island, an area with a high prevalence and intensity of chloroquine resistance, 158 cases of acute falciparum malaria were treated with chloroquine (1.5 g base over 3 days as an adult dose); there were 43 RII and 23 RIII responses. These patients were then treated with hydroxypiperaquine at a total dose of 1.5 g base over 3 days; fever and parasites cleared rapidly within 37.2 and 52.4 hours respectively. There were 3 late recrudescences among 64 patients followed up for 4 weeks (*36*). These could have been reinfections.

Hydroxypiperaquine is also an effective blood schizontocide against *P. vivax*. Given at doses of 0.9–1.2 g base over 2 days it produced parasite clearance in all of 718 cases, with a mean clearance time of 41.3 hours. Chloroquine, at a dose of 1.2 g base over 2 days, also led to parasite clearance in all the 356 patients so treated, with a mean clearance time of 37.9 hours (Xu Deyu, personal communication).

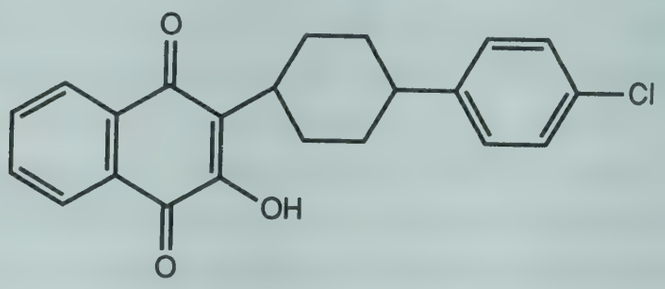
8.8 Hydroxynaphthoquinones

The antimalarial potential of the naphthoquinones was recognized in the mid-1940s, when they were shown to have both suppressive and curative action through their effect on the asexual tissue and blood cycles of avian and rodent malarias. Although Fawaz & Haddad (*37*) had successfully treated vivax malaria with intravenously administered lapinone (M-72350), the lack of activity of menoctone (WR 49,808) in patients infected with *P. falciparum*, presumably owing to poor absorption from the gastrointestinal tract, brought investigation of these compounds to a halt.

Recently, interest in this area has been renewed. One compound, BW 58C, has been shown to be highly active against *P. falciparum in vitro* and against *P. berghei* and *P. cynomolgi in vivo* (*38*). In the *P. yoelii nigeriensis*/mouse system, BW 58C showed causal prophylactic activity comparable to that of primaquine and, as a blood schizontocide, it showed no cross-resistance with chloroquine, mefloquine, pyrimethamine, primaquine, or sulfonamides. Clinical development of BW 58C was discontinued after Phase I trials, but a second hydroxynaphthoquinone, A566C (Fig. 11), is currently being

evaluated in the clinic for its potential for prophylaxis and treatment of malaria.

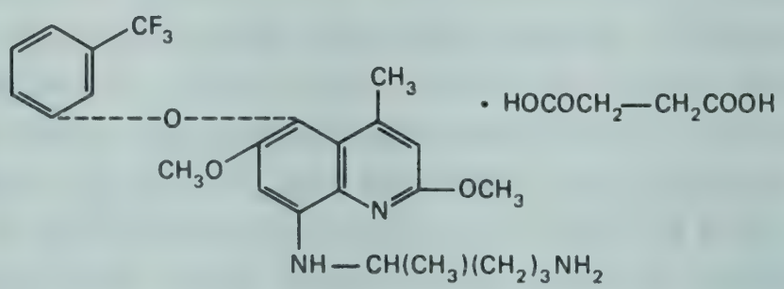
Fig. 11. A566C



8.9 8-Aminoquinolines

WR 238,605, an 8-aminoquinoline, is being developed by the Walter Reed Army Institute of Research (Fig. 12). It is 13 times more active as a hypnozoitocidal drug than primaquine, as measured by the dose required to obtain a radical cure of *P. cynomolgi* infections in monkeys. In contrast to primaquine, it also has appreciable blood schizontocidal activity. Preclinical studies on this compound are complete, and it is expected that Phase I clinical trials will be initiated in the very near future.

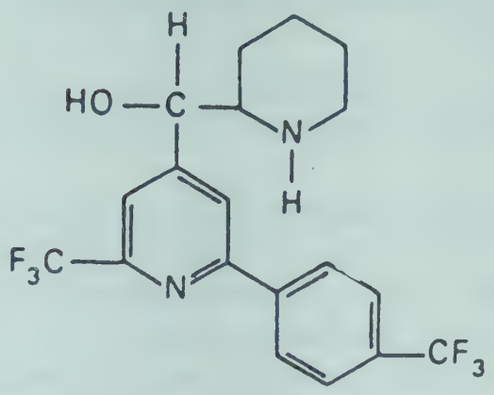
Fig. 12. WR 238,605



8.10 Pyridinemethanols

The most studied member of this group is WR180,409, which has been given the name enpiroline (Fig. 13). It is readily absorbed and rapidly distributed throughout the body. The drug has undergone extensive preclinical studies and has been tested both in volunteers with induced malaria and in patients with natural infections in Thailand. A single dose of 750 mg cured 17 of 20 naturally infected

Fig. 13. Enpiroline



Thai soldiers. *In vitro* studies indicate little cross-resistance with other drugs with the possible exception of mefloquine. However, development of this compound by the US Army has been discontinued.

8.11 Acridinones

These compounds were of interest because they have causal prophylactic as well as blood schizontocidal activity. Work on this series of compounds has, however, virtually stopped since floxacrine, the original lead compound, and several of its analogues have been shown to produce endarteritis in chronic toxicity studies. To date, no floxacrine analogues have been synthesized that separate the antimalarial activity from the inherent toxicity of these compounds.

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9. CONCLUSIONS AND RECOMMENDATIONS

9.1 Treatment policy

9.1.1 The elaboration of a policy for the treatment of malaria at the periphery should take into account:

—the status of the existing antimalaria services and the general health infrastructure;
—the efficiency and effectiveness of malaria information systems;
—the feasibility of introducing new treatment regimens, including availability, cost, and acceptability of the relevant drug or drugs; and

—the difficulties involved in changing to new recommendations, such as those arising from the time lag between making a recommendation and its implementation at all levels of the health services.

9.1.2 It is imperative that target populations be clearly identified for the purpose of focusing treatment activities of health services; such target populations should be appropriately and specifically defined.

9.1.3 Epidemiological paradigms should be developed by WHO for the purpose of assisting countries in developing antimalarial drug policies.

9.1.4 Governments should make decisions on registering new antimalarial drugs on the basis of a well documented need for their introduction and take steps to ensure that they are used appropriately.

9.2 Diagnosis

9.2.1 Programmes supporting health care initiatives should collaborate to develop practical schemes for the evaluation and management of patients with febrile illness. Such schemes should specify criteria for the use of particular drugs, general supportive care, criteria for referral, and requirements for laboratory evaluation.

9.2.2 Health services should critically evaluate deployment of laboratory services required for the management of malaria. Microscopical competence should focus primarily on the management of patients and only secondarily serve a surveillance role.

9.2.3 In areas where alternative (second- or third-line) antimalarials are required because of drug resistance, microscopical diagnosis is particularly important as an integral component of patient management, in order to minimize exposure to potentially toxic drugs and to target expensive drugs to the patients who need them.

9.2.4 Malaria control programmes should use laboratory methods that are economical; all alternatives to standard microscopical

examination of blood films must be judged as to their cost, the technical training required, and the sustainability of the methods.

9.2.5 Every effort should be made to minimize the potential for the transfer of bloodborne infectious agents occurring as a result of the preparation of blood smears for examination. Such efforts include:

—discouraging the reuse of lancets;
—mandatory use of effective sterilizing methods when reuse cannot be avoided;
—targeting the collection of blood films and minimizing the taking of blood samples for routine surveillance;
—training of all health staff in appropriate methods for protecting themselves from bloodborne infections;
—use of appropriate methods for the disinfection and disposal of contaminated laboratory supplies.

9.3 Treatment of uncomplicated malaria

9.3.1 In view of the evidence that amodiaquine is only marginally more active than chloroquine, and that it can produce toxic hepatitis and potentially lethal agranulocytosis, amodiaquine *should not* be used in malaria control programmes either for prophylaxis or even as an alternative treatment for chloroquine therapy failures.[1]

9.3.2 Severe cutaneous reactions to the sulfonamide component of mefloquine/sulfadoxine/pyrimethamine have been reported. In view of the additional risk and the fact that studies have indicated that the combination provides no therapeutic advantage over mefloquine alone, the triple combination is not recommended, either for treatment or for prophylaxis.

9.3.3 Because of its potential toxicity, cost, and long half-life, mefloquine should not be used for treatment where chloroquine or sulfadoxine/pyrimethamine are effective. Mefloquine should only be used following either microscopical or careful clinical diagnosis of *Plasmodium falciparum* infections known or strongly suspected to be resistant to chloroquine and sulfadoxine/pyrimethamine.

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[1] The Nineteenth Expert Committee on Malaria (unpublished WHO document WHO/CTD/92.1) recommended in November 1989 that the use of amodiaquine should be weighed against the risk of potential fatal side-effects.

9.3.4 In view of the increasing number of reports of neurological and psychiatric side-effects apparently related to the use of mefloquine either for prophylaxis or treatment, national health programmes and WHO should initiate a retrospective study of the epidemiology of this adverse reaction. The Organization should develop a monitoring system for the prospective surveillance of all major reactions to mefloquine as well as to other antimalarials, and assist endemic countries to establish or strengthen such systems.

9.3.5 Antirelapse treatment of *P. vivax* infections with primaquine should be limited to two categories of patients: those resident in nontransmission areas or areas with very low levels of transmission and those treated during an epidemic, when mass drug administration is combined with vector control measures. It is not necessary to provide antirelapse treatment routinely to a patient living in an endemic area; in case of relapse or reinfection, such patients should be treated with an effective blood schizontocide.

9.3.6 Primaquine, as a gametocytocide, should be reserved for the sterilization of *Plasmodium falciparum* infections in people moving to areas from which this parasite has been eliminated, but which are susceptible to its reintroduction, and as a component of emergency mass drug administration in epidemic situations.

9.4 Treatment of severe malaria

9.4.1 On the basis of pharmacokinetic data relating to the use of parenteral quinine, it is important, particularly for severe malaria, that a loading dose be used for initiation of treatment. However, it must be kept in mind that a high proportion of patients will have taken antimalarials before presenting for treatment. Addition of a loading dose to a pre-existing high blood level of quinine, and probably of mefloquine or chloroquine, could produce serious additive toxicity, particularly to the cardiovascular system. Before the loading dose is used, the treating physician should ensure, through screening of blood or urine where this is possible, or through careful history-taking, that the patient has not received quinine or chloroquine during the previous 12 hours, or mefloquine during the previous 24 hours.

9.4.2 Chloroquine should not be used for treatment when an infection has "broken through" chloroquine prophylaxis, or does not appear to be responding to chloroquine treatment, or if there is any doubt about the origin of the infection. Clinicians may prefer to use quinine in all cases of severe falciparum malaria because of the rapid spread of chloroquine resistance and the risk of newly emergent chloroquine resistance even when the infection has been acquired in a predominantly chloroquine-sensitive area of the world.

9.4.3 Intramuscular preparations of sulfadoxine/pyrimethamine have proved effective in preliminary clinical trials. This combination may have been overlooked because of unjustified assertions that it was slow-acting. Further clinical studies are needed in areas where *P. falciparum* is sensitive. At the levels of the health service at which intramuscular injections can be given, intramuscular sulfadoxine/pyrimethamine combinations could be valuable in the treatment of chloroquine-resistant falciparum malaria for patients who cannot swallow tablets.

9.4.4 Quinidine is more toxic and more expensive than quinine, and its possible therapeutic superiority is not yet needed. Whether in oral or parenteral formulations, it is recommended as an alternative to quinine *only* when quinine is not immediately available.

9.4.5 The risks associated with the routine use of blood transfusion in tropical areas are multiplying. If, in the treatment of patients with severe malaria, attempts to improve oxygenation and correct hypoxaemia with colloid infusions have failed, the assessment of the clinical condition (shock, cardiac failure, hypoxia) rather than an arbitrary haematocrit value should be used as the indication for transfusion.

9.4.6 Full or partial exchange transfusion for hyperparasitaemia is not recommended unless the availability of pathogen-free blood can be absolutely assured, the patient is severely ill as well as being hyperparasitaemic, and the clinical facilities are adequate.

9.4.7 Further efforts are required to identify safe and effective methods to treat malaria which are applicable at peripheral levels of the health service, when oral therapy is inappropriate, e.g., the use of suppositories, orogastric intubation, or subcutaneous injections.

9.5 Prophylaxis

9.5.1 Malaria infection in pregnancy may have various important deleterious effects on both the mother and the fetus. The most effective and operationally feasible methods to control these effects require definition in specific settings. In settings where placental parasitaemia is associated with low birth weight, and an effective antimalarial drug can be provided on a regular basis, chemoprophylaxis may be considered. In most areas, however, prompt therapy of malarial illness and of malaria-associated disease will be the most feasible objective.

9.5.2 No prophylactic regimen can be expected to give absolute assurance of protection, and most drugs used for prophylaxis are associated with some toxic side-effects. Therefore groups such as elderly individuals, very young children, and pregnant women should consider very carefully whether travel to malarious areas is absolutely necessary.

9.6 Monitoring

9.6.1 Adverse reactions to antimalarial drugs are an increasingly important determinant of drug use, as new drugs are introduced into operational use, and when antimalarials are used in combination or by persons taking other medications. Appropriate and simplified surveillance systems should be devised specifically for the early detection of adverse reactions occurring in malaria control activities. Such early detection should be concentrated in settings where new drugs are being used on a wide scale, or where there is a new application (dose, dosage form, combination) of an existing drug.

9.6.2 Monitoring of adverse reactions to malaria chemoprophylaxis in visitors and nonimmune residents in endemic areas is an important way of detecting potential toxicity of antimalarial drugs after they have been marketed. It is recommended that WHO coordinate the development of appropriate methods for monitoring adverse reactions in these populations and liaise with countries and institutions responsible for advising short-term visitors to ensure comparability and accuracy of adverse-reaction monitoring.

9.6.3 Malaria-endemic countries should be assisted in the development of simple and sustainable systems for the identification

and reporting of side-effects of antimalarials. WHO is requested to improve the dissemination of information on adverse reactions and to inform endemic countries when such reactions to antimalarials are detected.

9.6.4 The frequency of treatment failures should be carefully monitored and reported to health authorities as changes may indicate alterations in the epidemiological situation in an area or a change in drug sensitivity.

9.6.5 For routine patient management and monitoring of drug efficacy, *in vitro* drug sensitivity data are generally not required or useful, and the technical capacity to conduct the necessary assays is difficult to develop and maintain in malaria control programmes. The technique is useful, however, for specific research studies and for the determination of baseline susceptibility of *P. falciparum* to new drugs intended for introduction into an area.

9.7 Drug procurement and distribution

Supply, distribution, and quality control

9.7.1 More rational patterns of self-medication, such as "home treatment", should be encouraged. Clear instructions on dosage as well as clear, unambiguous guidance on when to seek further treatment should be provided, bearing in mind that the referral facility may be a day or more away.

9.7.2 WHO should assist countries in obtaining adequate quality control services for antimalarial drugs.

9.7.3 Countries susceptible to malaria epidemics should maintain adequate buffer stocks of antimalarials to deal with the initial phases of epidemics.

9.7.4 Research on population coverage and the cost implications of different drug distribution systems should be conducted in countries with different epidemiological situations and health care systems.

Cost considerations

9.7.5 The implicit use of cost as a rationing measure and for determination of level of use should be re-examined; other more appropriate measures for the control of drugs should be formulated.

9.7.6 If there are going to be charges for antimalarials by government programmes, such charges within any cost-recovery scheme should be commensurate with the target population's ability to pay, especially when the targets are women and children.

9.7.7 Research on health services utilization should be conducted in order to understand current practices among all segments of the population and to be able to estimate the impact of changes in health services organization and of increases in user charges for services.

9.7.8 The prices of new antimalarials should be kept as low as possible, within the purchasing power of endemic countries.

9.7.9 Since, in many cases, WHO contributes considerable financial resources to drug development, e.g., clinical trial support, the Organization should negotiate the unit price of any eventual product of such work with the pharmaceutical companies concerned.

9.7.10 WHO should investigate with companies the possibilities of differential pricing to enable the procurement of newer drugs by lower-income developing countries. An example would be application of higher prices in industrialized countries, particularly for travellers, to subsidize cheaper sales to developing countries.

9.7.11 WHO should strengthen its assistance to governments in procuring drugs at low cost; the Organization should also ensure that governments are aware of the availability of such assistance.

9.8 New drugs

9.8.1 Recent clinical data on halofantrine indicate that it is an effective drug for the treatment of chloroquine-sensitive and resistant *P. falciparum*. There is, however, concern about the great variations in bioavailability of the currently available oral formulation. In view of its potential operational importance, which

may include its use for the treatment of mefloquine-resistant *P. falciparum*, halofantrine *should not* be deployed as a first-line drug at the peripheral levels of the health care system. Its use should be restricted to treatment at higher levels of the health services. The drug should *only* be used for treatment of acute malaria attacks that are likely to be due to multidrug-resistant falciparum malaria, following either microscopical or careful clinical diagnosis. Governments should be encouraged to legislate strict control of the importation, distribution and utilization of the drug.

9.8.2 The artemisinin derivatives are very promising alternatives for the treatment of severe and complicated malaria. However, it is necessary to obtain more experience with these drugs in different epidemiological situations. Controlled clinical studies of the available formulations—including oral, parenteral, and suppository forms—should be undertaken in a number of malaria-endemic countries to compare the efficacy and safety of artemisinin and/or its derivatives with the appropriate available drugs.

9.8.3 While the available data on dose-finding and formulation are relatively exhaustive, there is still a need to assess associations or sequential use of artemisinin derivatives with other drugs in order to arrive at a curative regimen—one that not only clears parasitaemia but also prevents recrudescences. In this context, emphasis should be placed on relevant drug interaction studies.

9.8.4 TDR/CHEMAL[1] should intensify its efforts to bring an intramuscular formulation of an appropriate artemisinin derivative to registration in a variety of countries as a matter of urgency, and should begin the planning of clinical trials at an early date.

9.9 Malaria treatment information

9.9.1 Any attempt to improve the rational development of malaria treatment must include the production and dissemination of current and locally relevant information about malaria for prescribers and the public at large. This information, about the diagnosis of malaria, the effectiveness of drugs and their safety, must

[1] The Scientific Working Group on the Chemotherapy of Malaria, of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

be understandable to the populations at risk and those responsible for their health care.

9.9.2 Prescribers and the public at large need to be provided with objective up-to-date information on the treatment of malaria, and in particular on the effectiveness and safety in the local situation of the drugs in use.

9.9.3 Since malaria chemotherapy is, of necessity, constantly changing, reports that embody recommendations on the choice and use of antimalarials should carry an indication that their validity is limited in time; a date should be specified at which they should be revised or brought up to date by a supplement.

9.9.4 The maternal and child health or essential drugs programmes in many countries could be used to distribute not only drugs but information as well. Malaria guidelines and information on the risks of serious side-effects should be included in prescribers' manuals and drug ration kits. Such information should be discussed at prescriber training seminars. Other means that could be used to reach the public at large include the media, literacy classes, advertising, schools, and religious institutions.

9.9.5 Rural storekeepers, market sellers, and other unofficial distributors should be provided with simple information on the use of antimalarials, including indications for use, appropriate dosage, and referral criteria.

9.10 Research priorities

9.10.1 Since many patients who attend health services for antimalarial treatment have already taken drugs themselves or received drugs from other facilities, the interaction of drugs which may be sequentially administered should be studied both kinetically and dynamically. Such associations would include quinine and mefloquine, artemisinin analogues and mefloquine, quinine and sulfonamides, and chloroquine and sulfonamides.

9.10.2 Intensive studies should be carried out on the interaction between antimalarials and other drugs commonly coadministered with them, e.g., mefloquine, quinine or chloroquine with metoclopramide (or other antiemetics), beta-blockers, and digoxin.

9.10.3 Field studies are required in areas where a decline in chloroquine use can be quantified to determine whether there is a positive increase in sensitivity to that drug and whether this sensitivity is significant in terms of effect on treatment and stability.

9.10.4 Research on compounds that have the apparent ability to diminish the rate of chloroquine efflux from malaria-infected cells, such as various calcium-channel antagonists and the antidepressant desipramine, has given rise to optimism concerning the potential for "reversal" of chloroquine resistance. In view of the critical importance of such "reversal", further laboratory research into it should be stimulated and supported. The combination of chloroquine and resistance "reversers" should not be used for human clinical trials at present.

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The development of common guidelines on the use of antimalarial drugs is made particularly difficult by the rapidly changing epidemiological patterns of malaria, and their variability even within a country. Recognizing this, the WHO Scientific Group on the Chemotherapy of Malaria, in the present report, has attempted not only to make recommendations for the use of specific drugs, but also to provide the technical information needed to evaluate and, if necessary, adapt those recommendations. The report therefore discusses the factors that need to be considered in developing and implementing a policy on the use of drugs in malaria. The management and treatment of both severe and uncomplicated malaria are dealt with in detail, and more general topics, such as estimating the amounts of drugs needed, their procurement, and monitoring systems, are also considered. A separate section deals with antimalarial drugs currently under development.

The report is addressed primarily to middle-level planners and administrators responsible for malaria services, but research workers, clinicians and primary health planners will also find it a useful guide to the factors that influence the choice of drugs for the treatment of malaria.

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